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ARCHIVES OF DISEASE IN CHILDHOOD.

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THE LEUCOCYTE COUNT IN RHEUMATIC HEART DISEASE IN CHILDHOOD.

BY

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(From the University Centre of Cardiac Research, General Hospital, Bristol.)

This investigation was undertaken to see if the leucocyte count in rheumatic heart disease might serve as a useful index of activity of the infective process.

Cabot[1] stated that a leucocytosis of about 14,000 per c.mm. was the rule in children suffering from acute rheumatism. Ewing[2] considered that mild cases of rheumatism showed no leucocytosis, but that with fever and swelling of the joints a leucocytosis from 10,000 per c.mm. occurred. If the leucocytosis be greater than 20,000 per c.mm. it indicates the presence of some complication. The leucocytes return to normal in defervescence. Quoting Türk, he stated that with a total count of under 10,000 per c.mm. the differential count is not disturbed, but that with a greater leucocytosis than this the proportion of polymorphonuclears is increased, and this after defervescence, is followed by an eosinophilia. Macalister[3] in 1909 found that 8 cases of chorea all showed an eosinophilia to a greater or lesser extent. This was not found to be the case in acute rheumatism, and he considered that this indicated different causes for the two conditions. Bosc and Carrieu[4], from an examination of 12 cases of acute rheumatism, concluded that this is usually associated with a leucocytosis. There is a relative mononucleosis with a greatly increased number of 'medium, large and very large mononuclears' and occasionally of lymphocytes. In convalescence the mononucleosis persists and is accompanied by an eosinophilia. Leopold[5] in 1914 found in 20 cases of chorea an eosinophilia of from 1–16 per cent.; higher in second attacks than in the first. Berger[6] made a series of counts in 40 children with chorea aged from 7–14 years. He found that all but 5 of these showed an eosinophilia at some stage or other. The highest eosinophilia found was 26 per cent. of the total count, and the lowest 0 per cent. The average for the series was 7·6 per cent. The rise and fall of the eosinophilia was unconnected with any change in the clinical course of the illness. No other cause for an eosinophilia could be demonstrated. Swift, Miller and Boots[7], by repeated white cell counts, found that cases with a single 'monocyclic' attack of polyarthritis showed a slight leucocytosis which rapidly fell with anti-rheumatic therapy, and showed a light temporary rise on its discontinuance. In cases with a relapsing arthritis the leucocytes tended to remain above normal for a longer period, and were less influenced by therapeutic measures. In cases with a pronounced cardiac lesion, half of whom showed nodules, there was a persistent leucocytosis with occasional falls to normal, followed later by a rise again, and almost entirely uninfluenced by drugs. They conclude that :—

(1) Rheumatic fever is associated with a leucocytosis. (2) The leucocyte curve gives some idea of the severity and duration of the infection. (3) Patients with arthritis and exudative phenomena show a more marked leucocytosis than those with a proliferative reaction, such as myocarditis and nodules. (4) A leucocytosis depressed by anti-rheumatic drugs, indicates a mild infection of short duration. The persistence of the leucocytosis in spite of drugs, or its return on the discontinuance of the administration of the drug, indicates a more persistent infection. (5) Relapses are heralded by a rise in the leucocyte count.

Gulland and Goodall[8] reported in chorea a slight leucocytosis and, despite contrary reports, no evidence of the constant, or even usual, occurrence of an eosinophilia. In acute rheumatism they found a leucocytosis of 12,000 to 15,000 per c.mm., very rarely exceeding 20,000 per c.mm.

Wilson and Kopel[9] found that the average leucocyte count in children with a history of previous rheumatic infection, was 7,000 per c.mm.; in children with evidence of an organic

cardiac lesion was 7,700 per c.mm.; in children with evidence of an active infection was 9,000 per c.mm. They considered that the leucocyte count is of value as an index of activity.

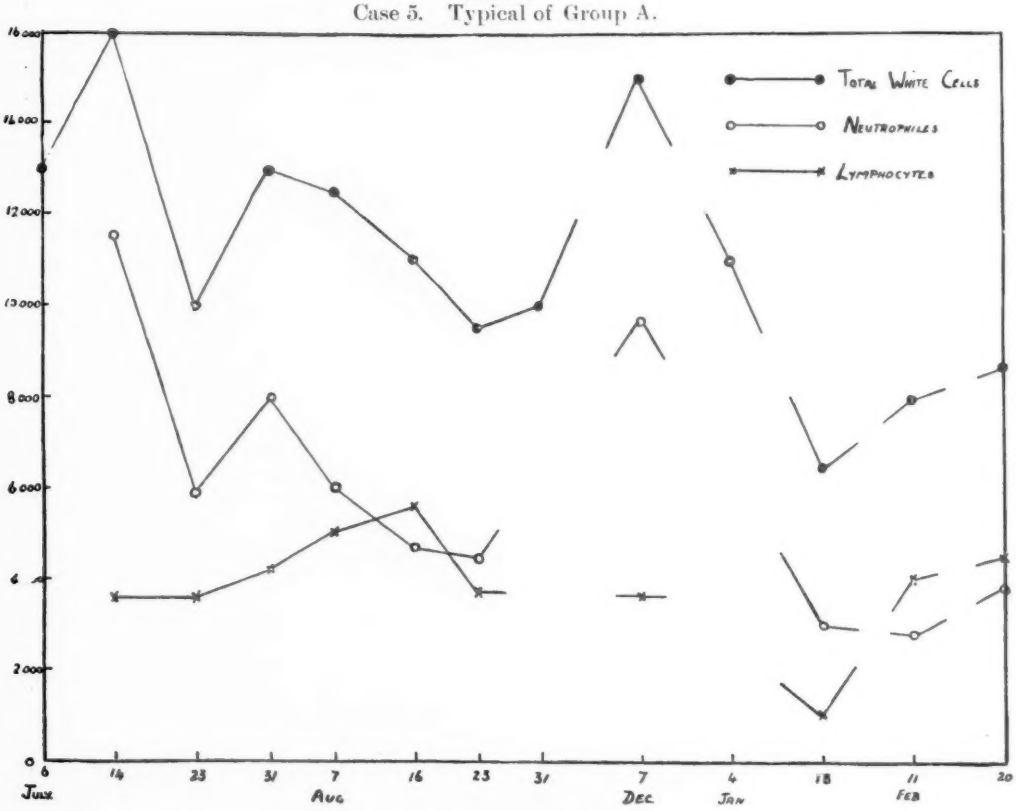
Thayer[10] reported that in 24 children with rheumatic carditis 20 showed a leucocytosis of over 10,000 per c.mm.; 11 over 20,000 per c.mm., and 5 over 30,000 per c.mm.

Piney[11] stated that acute rheumatism is associated with a slight leucocytosis which never exceeds 15,000 per c.mm. This leucocytosis often does not reappear in relapses. At the onset the eosinophiles are diminished, but reappear later and then persist throughout the rest of the illness.

Present Investigations.

In the present series repeated white cell counts were made on 41 children, 239 counts in all being made. All the cases were under the action of salicylate in some form or another, as it was not considered advisable to suspend the use

CHART I.
Case 5. Typical of Group A.



of it for the purpose of investigation. The blood was collected as nearly as possible at the same time of the day on each occasion, and all the counts were done personally. Differential counts were done in most cases. At first the neutrophils were divided into myelocytes, metamyelocytes, band forms and adult polymorphonuclears after Schilling[12], but it was seen that there was no obvious shift to the left or right, and this method was dropped in the later counts, the cells being divided simply into neutrophils, eosinophils, basophils, lymphocytes and monocytes. Various stains were used, but Leishman's was finally adopted as being most serviceable.

Results.

The cases have been divided clinically into six groups.

Group A. (*Cases* 1–6). Six cases, seen in a first acute attack of arthritis or chorea, associated with evidence of carditis.

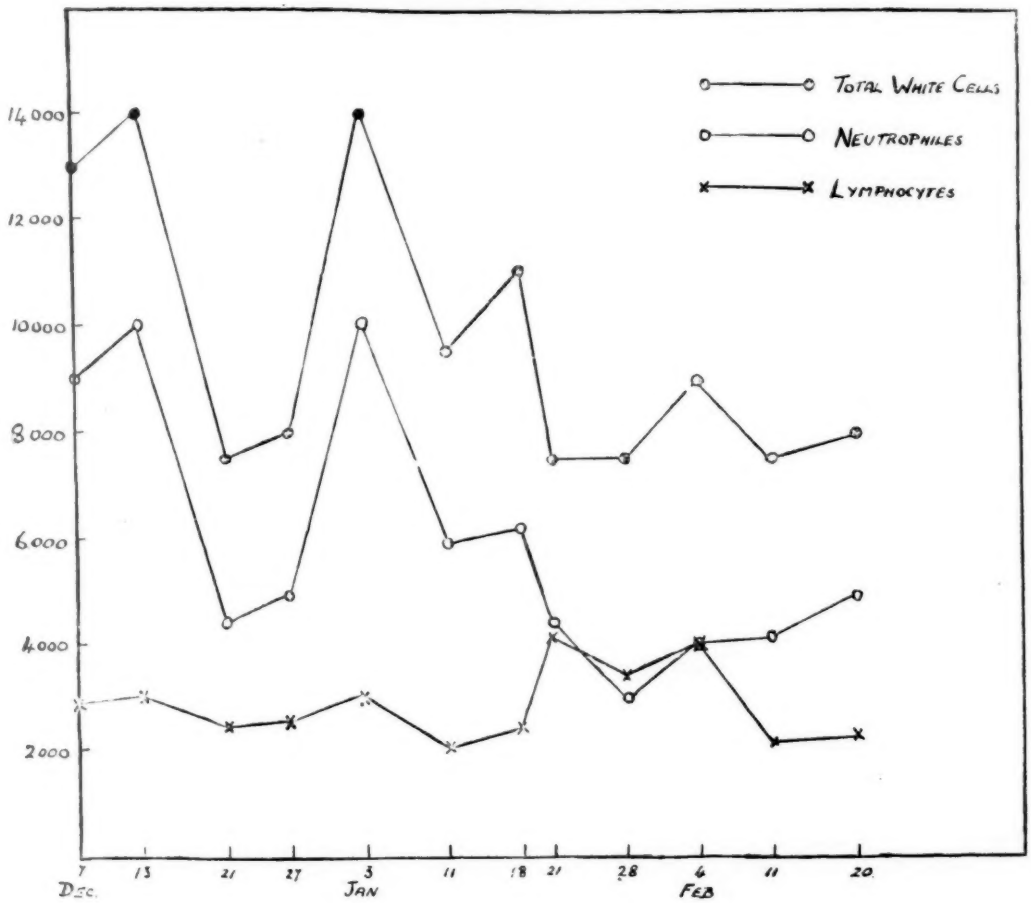
The average highest total count was 15,500 per c.mm.

The highest count made was one of 27,000 per c.mm. It was found in Case 2 late in the illness, when clinically improved.

The lowest count at the onset was 9,000 per c.mm., observed in Case 3 six days after the onset of arthritis. The count fell in 3–4 weeks to somewhere near the normal level, as determined in later examinations.

CHART II.

Case 10. Typical of Group B.



The main increase in the count is due to an increase in the neutrophils, although not entirely so, as the highest percentage of neutrophiles was 72 per cent. This tends to be followed, as the count falls, by a lymphocytosis.

There was no marked increase in the monocytes at any stage except in Case 5, which in convalescence showed a monocyte count as high as 9 per cent. of the total cells.

Case 2 in conjunction with, and preceding, the lymphocytosis showed a gradual eosinophilia reaching 7 per cent. of the total.

Chart I shows the curve of Case 5 which is typical of the group.

Group B. (*Cases* 7–10.) Four cases, seen in an acute exacerbation of a carditis whether associated with other rheumatic manifestations, or not. One of the cases was followed through two relapses.

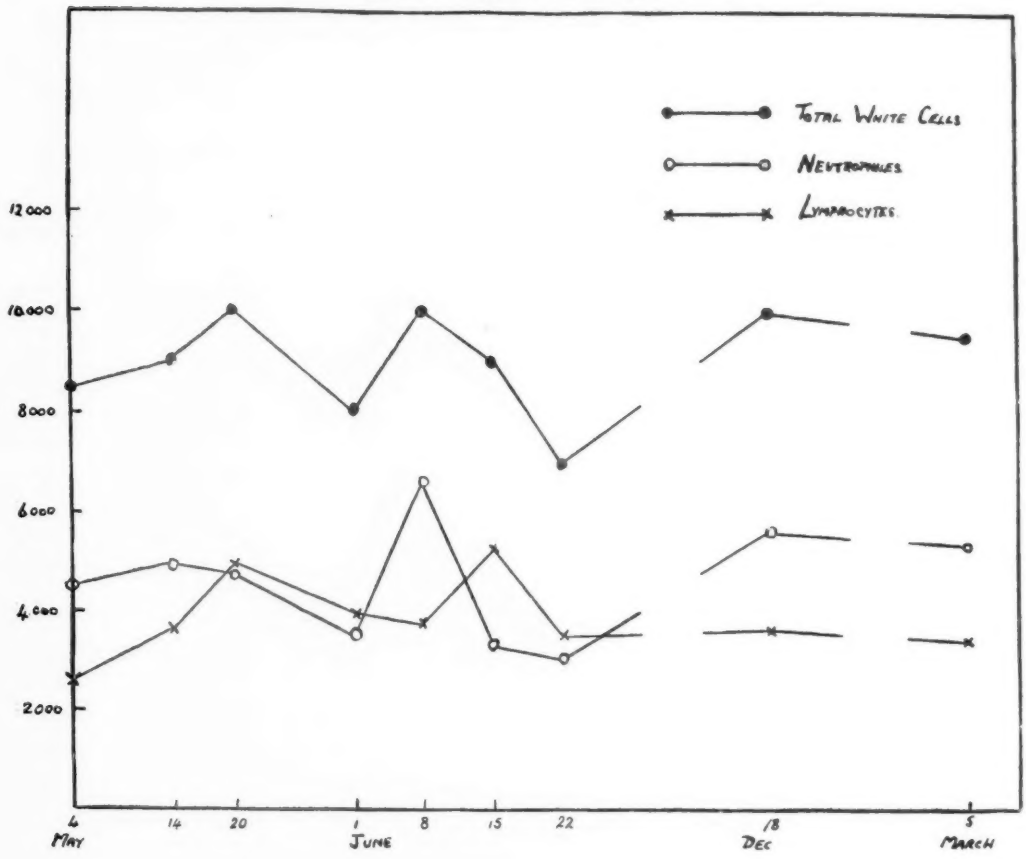
The average highest total count was 12,900 per c.mm.

The highest count observed was 28,000 per c.mm., again at the end of a recrudescence in Case 7. The highest count observed in Case 8 which terminated fatally, and was confirmed post mortem, was 17,800 per c.mm. a few days before death.

The lowest count observed, while the patient was acutely ill, was 7,000 per c.mm. in Case 9. In this case the count later rose to 11,000 per c.mm., and still later, after discharge from hospital, to 12,000 per c.mm.

CHART III.

Case 16. Typical of Group C.



The increase was mainly in the neutrophils, the highest percentage, apart from the late rise in Case 7 being 72 per cent.

There was no definite lymphocytosis or eosinophilia. The highest percentage was 5 per cent., and these cells fluctuated quite independently of the other cells. There was no monocytosis.

Chart II shows the curve of Case 10 and is fairly typical.

Group C. (Cases 11–26). Sixteen cases showing clinical evidence of a subacute and smouldering infection, such as nodules, slight fever, "sub-chorea," or occasional pains, and evidence of a cardiac lesion. Case 12 was followed through two relapses.

The average highest total count observed was 11,700 per c.mm.

The highest count made was 18,000 per c.mm. in Case 12 and this also was late in the first relapse.

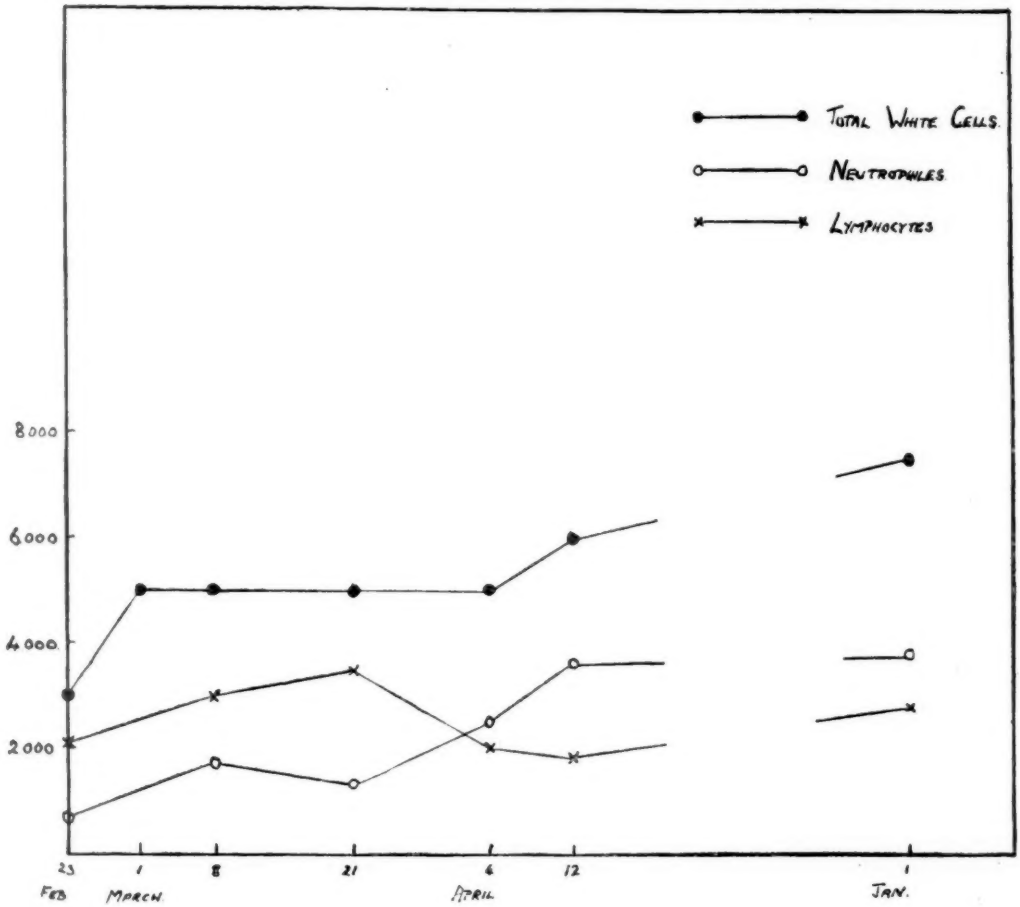
The lowest count observed when first seen (with the exception of one case) was 7,800 per c.mm. in Case 11, in which the count later rose to 9,800 per c.mm.

The count fell on improvement in varying times. The differential counts showed no definite curves. There is occasionally a tendency to a relative lymphocytosis as the count falls.

The eosinophils varied from 5 per cent. to 7 per cent. with no obvious relationship to the rest of the blood picture, or to the clinical condition.

CHART IV.

Case 22. Showing the leucopenia which was observed in this case.



A typical curve, that of Case 16, is shown in Chart III. The one case referred to above (Case 22) showed a leucopenia of 3,000 per c.mm., with a relative lymphocytosis of 70 per cent. when first seen. On improvement the count gradually rose to normal as shown in Chart IV. There was no clinical distinction between this and the other cases throughout the illness.

Group D. (*Cases* 27–37). Eleven cases admitted to hospital under the suspicion of having an active infection, but which on further investigation showed no definite evidence of this. All showed signs of cardiac involvement.

The average highest total count was 8,700 per c.mm.

The highest counts observed were 13,000 per c.mm. in cases 28 and 37.

The lowest count made, except after discharge, was 6,000 per c.mm.

There was no constant fall in the count on improvement. No significant variations in the differential count were noted. There was no eosinophilia, the highest count observed being 6 per cent. on one occasion in Case 35.

Case 38 had an average monocyte count of 7·5 per cent. No other case showed any monocytosis.

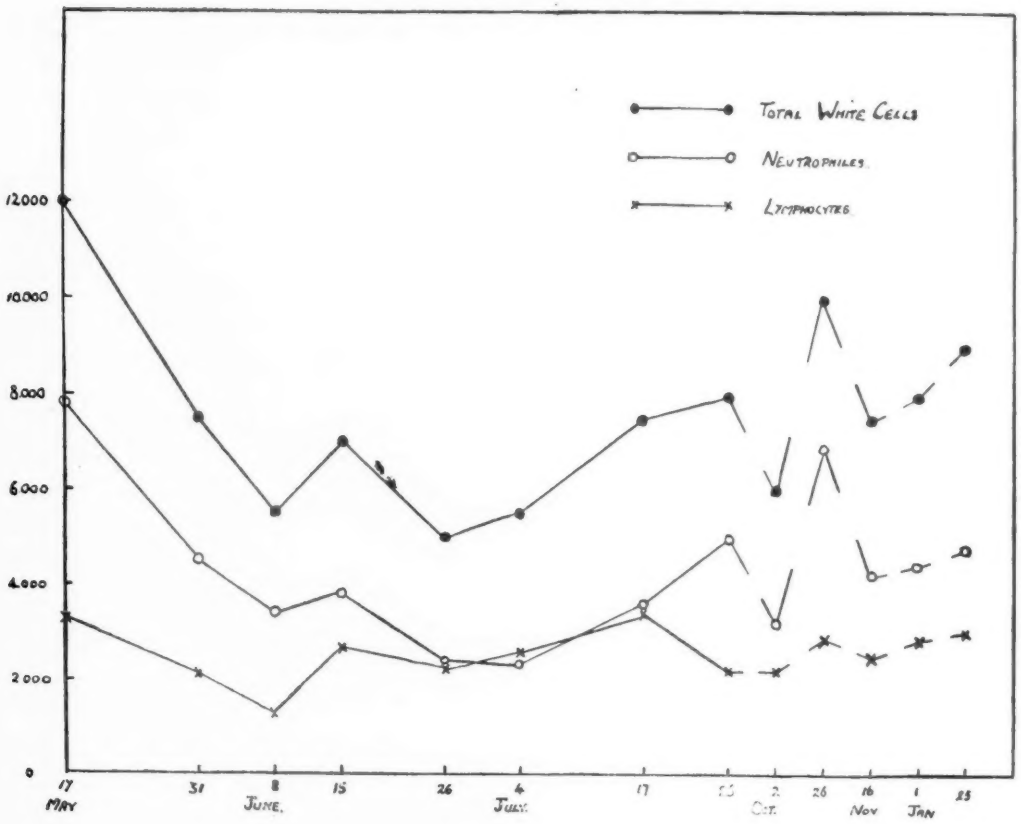
Chart V is of Case 32 and is a curve typical of the group.

Group E. (*Cases* 38 *and* 39). Two cases of chorea with no clinical evidence of carditis.

One of these cases showed a leucocytosis of 11,000 per c.mm. rising while under observation to 15,000 per c.mm. The other case had a count of 7,000 per c.mm. There was no change in the differential count.

CHART V.

Case 32. Typical of Group D.



Group F. (*Cases* 40 *and* 41.) Two cases of chronic rheumatic heart disease with no suspicion of active infection.

The highest count observed was 8,000 per c.mm. in Case 41. The count remained at a fairly constant level while under observation (see Chart VI). The eosinophils varied from 1 to 6 per cent.

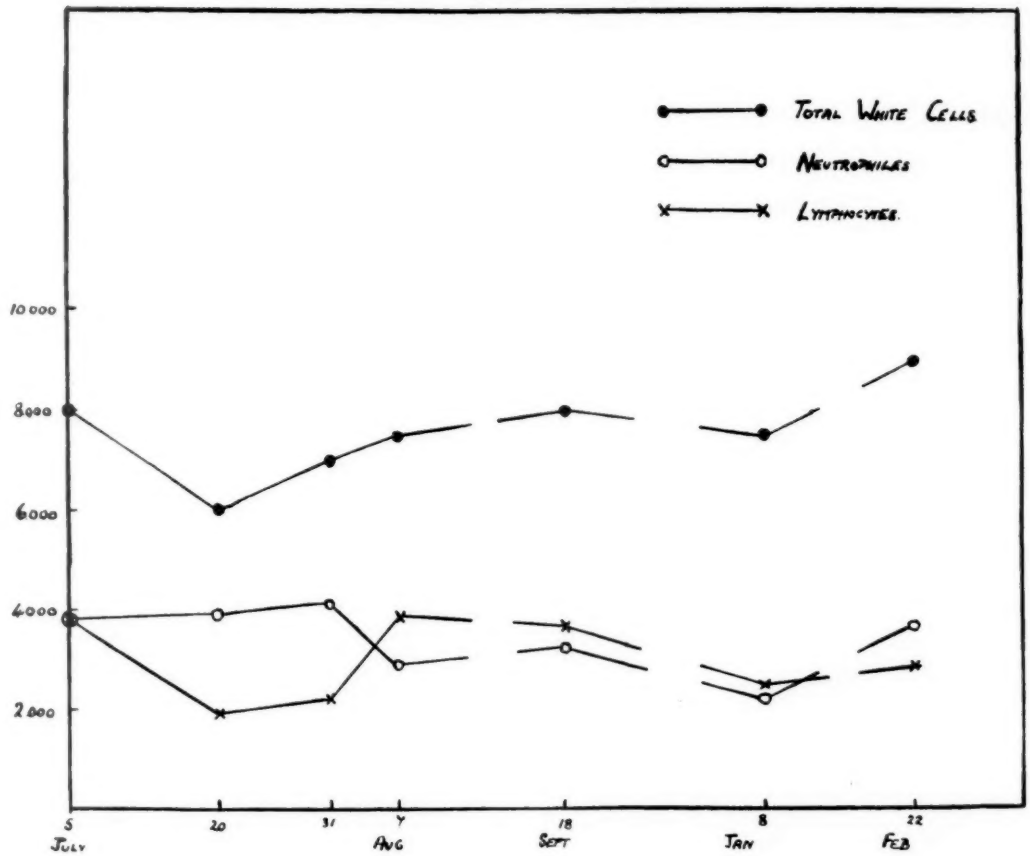
Chorea. Those cases showing definite chorea were further examined together for any evidence of an eosinophilia. There were 10 cases in all. In 6 of these the highest percentage of eosinophils recorded was 4 per cent. Of the other 4 cases the highest percentage observed in Case 21 was 8 per cent., fairly late in the course of the illness. Case 16 on two occasions had 6 per cent. of eosinophils. Cases 12 and 23 showed an eosinophilia of 7·5 per cent. and 10 per cent. respectively, occurring with a relative lymphocytosis.

Discussion.

From these figures it would appear that acute rheumatic carditis is associated with a mild leucocytosis, with a neutrophile increase. The total cells fall fairly early in convalescence and there sometimes occurs a post-infective lymphocytosis which is often accompanied by the usual eosinophilia (Piney[11]). The leucocytosis recurs with relapses. This leucocytosis is however insufficiently marked and falls to within normal limits apparently in advance of clinical improvement, so that it is of little value as a practical index of activity

CHART VI.

Case 41. Typical of Group F.



of infection. Although repeated normal white cell counts would rule out any acute activity, a single count is of no value : moreover the repeated counts would not appear likely to help in the difficult question of the advisability or not of further convalescent treatment. Further, as Fletcher and Mitchell[13] have shown, in children the fluctuations of white cells are even more marked than in adults as demonstrated by Sabin[14] and her co-workers, and by Medlar[15]. One is therefore forced to conclude that the white cell count is of no practical value as an index of activity in rheumatic heart disease in childhood.

As regards chorea, no very strong evidence of an eosinophilia is forthcoming. The only eosinophilia observed would appear to be that associated with a post-infective lymphocytosis, and in this, as in other respects, the leucocytosis in chorea does not differ from that in other rheumatic manifestations.

Summary.

1. Acute rheumatic carditis is associated with a slight leucocytosis (12,000—15,000 per c.mm.).

2. This is mainly due to a neutrophile increase.

3. Subacute smouldering infections show a varying and less constant leucocytosis.

4. The leucocyte count is of no value as an index of activity in rheumatic heart disease.

5. There is no evidence of an eosinophilia in chorea.

My thanks are due to Dr. Carey Coombs for his help and advice.

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APPENDIX.

Group A. Case 5.—Male aged 11. 30.6.28. Acute polyarthritis. 5.7.28 Pancarditis. Gradual improvement till discharge 3.9.28. ? slight relapse at the end of November, 1928. No previous attack. (*See* Chart I.)

Group B. Case 10.—Male aged 12. November, 1924, first attack of acute rheumatism. Admitted 7.12.28 with arthritis, nodules and a severe pancarditis. Very slow improvement. Discharged 23.2.29. (*See* Chart II.)

Group C. Case 16.—Female aged 11. September, 1927, Choreic movements first noticed. Improved for a time but relapsed recently. Admitted 15.5.28 with chorea; heart not enlarged, apical systolic bruit. Improved. Discharged 28.7.28. (*See* Chart III.)

Case 22.—Exhibited a leucopenia. Female aged 10. First attack of rheumatic fever, May, 1927. Scarlatina January, 1928. Since discharge from fever hospital joint pains. Admitted 21.2.28 with fever and pallor. Heart enlarged with apical systolic bruit and accentuated pulmonary second sound. Fever tended to persist. Gradual improvement. Discharged 19.4.28. (*See* Chart IV.)

Group D. Case 32.—Female aged 9. Admitted 2.5.28 with 2 years history of vague joint pains. Very slight chorea. No fever. Heart slightly enlarged with apical systolic bruit. Improved. Discharged 26.6.28. (*See* Chart V.)

Group F. Case 41.—Female aged 9. Rheumatic carditis November, 1927. Admitted 26.6.28 for tonsillectomy in quiescent stage. Operation 2.7.28. No post-operative reaction. (*See* Chart VI.)

CONGENITAL VALVULAR OBSTRUCTION OF THE URETHRA.

BY

OSWALD ADDISON, F.R.C.S.

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Since Langenbeck[1], in 1802, first described a case of congenital valvular obstruction of the urethra, similar cases have been recorded from time to time as post-mortem findings, but little attention has been paid to the condition from the clinical aspect.

To Professor Young[2] of Johns Hopkins Hospital belongs the credit from making the first clinical diagnosis of valvular obstruction, and successfully operating on the patient, a boy of 17. The case was recorded at the Johns Hopkins Hospital Medical Society in 1913. In 1919 Young, Frontz, and Baldwin[3] reported twelve cases in eight of which operation was carried out successfully, and recently Young and McKay[4] have published a further account of the condition with a total of twenty-one cases, of which fifteen were successfully operated on at the Brady Urological Institute, Johns Hopkins Hospital.

My attention was first called to this condition by seeing the specimen from Dr. Hutchison's patient reported by Poynton and Sheldon[5]. This specimen led me to make a diagnosis in the cases reported below, one of them (Case 1) having been mentioned in the article by Poynton and Sheldon.

Professor Young[3] describes three types of valve (Fig. 1).

Type 1. Ridge lying on the floor of the urethra continuous with the verumontanum, which takes an anterior course and divides into two fork-like processes in the region of the bulbo-membranous junction. These processes are continued as thin membranous sheets directed upward and forward, and may be attached to the urethra throughout its entire circumference. In the majority of cases of the general type the fusion of the valves anteriorly is not complete, there existing at the front a slight separation of the folds.

Type 2. In the second general type, there occurs a more or less cylindrical ridge similar to that found in the preceding type, with the exception that it passes from the upper aspect of the verumontanum towards the internal sphincter, where it divides into two fork-like processes which are continued as membranous sheets attached to the urethra just outside the internal sphincter in a manner similar to that described in the preceding type.

Type 3. There is a third type which has been found at different levels of the posterior urethra and which apparently bears no such relation to the verumontanum as the types just described. This was first mentioned by Jarjavay[6] who described it as an iris valve. This was attached to the entire circumference of the urethra, there being a small opening in the centre. Incomplete varieties of this type have been described, the most common being a more or less crescentic or semicircular fold crossing the urethra and being attached either to the roof or floor.

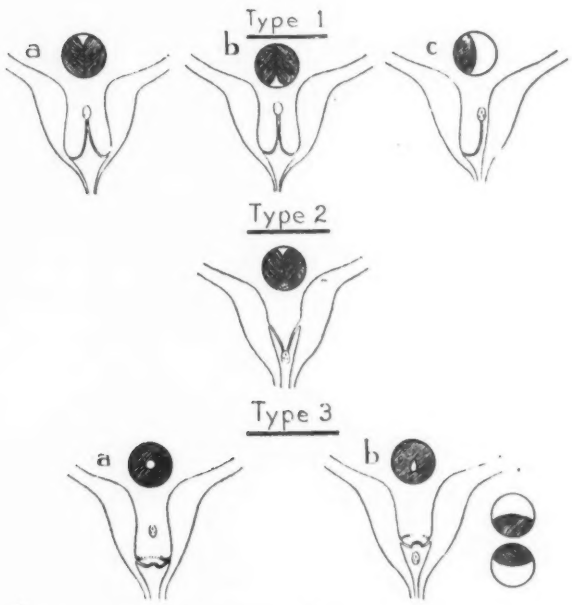

Fig. 1. A diagram showing the three types of congenital valves of the posterior urethra. Type 1: a, Two bifurcated valves springing from distal portion of verumontanum. b, Two fused valves in same position. c, A unilateral valve in same position. Type 2: A bifurcated valve extending from proximal portion of verumontanum to lateral sides of prostatic urethra and roof. Type 3: a, Iris valve below verumontanum. b, Iris valve above verumontanum. The shaded circles represent the cystoscopic field seen in the region of valve. The internal sphincter and the prostatic urethra are shown to be dilated and the region of the membranous urethra is indicated. (*By courtesy of Prof. Young from Surg. Gyn. and Obstet., 1929, XLVIII, 517*).

Author's Cases.

Case 1. S. W., a boy originally admitted under Dr. Poynton in January, 1926, age 2 years and 10 months. The case has been described in the Archives of Disease in Childhood[5]. He was admitted for wasting. He had always been delicate and complained of great thirst.

On examination the bladder was found to reach up to the umbilicus, and there was constant enuresis; the urine was acid, contained a cloud of albumen and much pus, and on culture grew Bacillus coli. Blood urea = 104 mgrm. per 100 c.cm. On cystoscopy the bladder was seen to be sacculated and trabeculated, and showed signs of chronic cystitis. There was no dilatation of the ureteric orifices. As there seemed to be some obstruction about the position of the compressor, bougies were passed and the urethra dilated as much as possible. Patient left the hospital very little improved.

He was re-admitted to hospital in June, 1927, in the same condition as in 1926. The bladder was up to the umbilicus and the urine continuously dribbling away.

Blood urea	60 mgrm. per 100 c.cm.
Urea concentration, 24 hours	85%
After urea 1st hour	1·08
2nd hour	2·45
3rd hour	0·05

The urine contained pus and albumen and gave a profuse growth of B. coli.

On June 26th the bladder was opened and with a head light a good view of the internal meatus was obtained. The internal meatus and prostatic urethra were seen to be dilated, but it was not possible to see the whole length of the prostatic urethra. No obstruction was seen. Bougies were passed through the internal meatus, and the urethra dilated as much as possible. The wound healed quickly except that an intermitent supra-pubic fistula formed, in spite of which patient was able to pass water naturally, with a good stream.

In January, 1928, patient was re-admitted for closure of the fistula. The fistula was excised and the opportunity taken once more to dilate the urethra by passing bougies *via* the internal meatus. The supra-pubic wound was slow to close but ultimately healed soundly, and patient was able to pass a good stream of urine.

After leaving hospital the boy's general health improved considerably and his thirst became much less, but he still remained very pale and did not appear to be very strong.

In November, 1928, he was re-admitted for tonsillectomy and the opportunity was taken to examine the condition of the bladder and kidneys. Urine was passed with a good stream but there were four ounces residual urine. A profuse growth of B. coli was obtained. Blood urea examination done on three occasions varied from 74 to 110 mgrm. per 100 c.cm.

Urea concentration test:

	Urea %	Vol. c.cm.
Before urea	1·52	—
After urea 1st hour ...	1·50	44
2nd hour ...	1·45	65
3rd hour ...	1·35	70

On cystoscopy the bladder showed signs of mild chronic cystitis. There was much trabeculation and sacculation. The ureteric openings were not obviously dilated but no contractions were seen. Catheters were passed up both ureters and 10 c.cm. of sodium iodide was injected into each. The pyelogram showed the catheters curled up in enormously distended ureters and a high degree of distension of the pelvis and calyces of both kidneys (Fig. 2).

In June, 1929, the boy's height and weight were 3ft. 7¼ in., and 34lb. respectively at the age of 6 years, 4 months.

Case 2. A. G., male, aged 8 years and 8 months, admitted to hospital, October, 1927.

History of bladder trouble for four years getting worse for four or five months. Straining on trying to pass water, poor stream, water dribbling away. Frequency during day five minutes to three hours. Nocturnal incontinence.

The boy's general condition seemed to be pretty good though he was rather pale. The bladder was distended and reached up to the umbilicus. The kidneys could not be felt and there was no tenderness in the loins. On attempting to micturate the urine only trickled away. The urine on examination showed a trace of albumen, many pus cells and a profuse growth of B. coli. Sp. Gr.=1020. Blood urea=30 mgrm. per 100 c.cm.

Urea concentration test:

	Urea %	Urine c.cm.
1st hour	1·05	148
2nd hour	0·70	137
3rd hour	1·15	50

On October 20th through a mid-line supra-pubic incision the bladder was exposed and stripped down from the back of the pubis. The prostatic urethra was exposed beneath the pubic arch and opened. A good view of the prostatic urethra was obtained but no valves or obstructions were seen. The veru montanum appeared to be very large and inflamed, and was touched with the cautery, as it was thought possible that it might have caused a reflex spasm of the compressor. Bougies were passed through the opening and down the urethra. The opening in the urethra was closed and a drain placed in the bladder. With daily irrigations of the bladder the boy's general condition improved greatly and in March the urea concentration test showed:—

	Urea %	Urine c.cm.
24 hours urine	2·41	
1st hour	2·31	71
2nd hour	2·72	68
3rd hour	2·90	85

Unfortunately a supra-pubic fistula formed and showed no signs of closing. On May 10th, 1928, the fistulous track was separated with great difficulty from the back of the pubis and followed to the prostatic urethra. The track was excised and the opening in the urethra closed. The fundus of the bladder was opened and the urethra was once more dilated as fully as possible by bougies passed through the internal meatus. A drainage tube was put into the bladder, and the space in front of the bladder down to the urethra was packed with gauze soaked in flavine to allow the opening in the urethra to close securely before becoming adherent to the pubis. The wound healed without trouble and the boy left the hospital able to pass a good stream of urine.

He was re-admitted to hospital in April, 1929, for investigation of renal functions, etc. The general condition of the patient was greatly improved, the supra-pubic scar was sound, and he was able to pass a normal stream of urine.

The urine was acid sp.gr. 1020–1028 and still heavily infected with B. coli. Blood urea was 39 mgm. per 100 c.cm.

Urea concentration test:

	Urea %	Volume c.cm.
Before urea	3·71	
1st hour	2·91	42
2nd hour	2·76	58
3rd hour	2·64	29

Cystoscopic examination showed much trabeculation and sacculation, very slight evidence of chronic cystitis. Both ureteric orifices gaping a little. Pyelography with sodium iodide showed slight degree of hydronephrosis of both sides (Fig. 3).

Case 3. N. J., male; aged 9½ years, admitted to hospital October 20th, 1928, with a history of incontinence of urine day and night since birth. The water has always been quite thick and foul smelling; thirst very troublesome for years. Has had no headache, nor vomiting, and has not complained of pain, but appetite is very poor and he seems to be losing weight.

The boy's general condition appeared to be fairly good. The bladder was up to the umbilicus and there was some tenderness over the right kidney, but neither kidney could be felt. On attempting to pass urine only a fine trickle escaped from the penis, and twenty ounces residual urine were found on passing a catheter. The urine was acid and contained stringy muco-pus, and a trace of albumen; it was infected with B. coli. Blood urea = 89 mgrm. per 100 c.cm. The urea concentration test showed:

	Urea %	Vol. c.cm.
Before urea	0·85	—
1st hour	0·91	43
2nd hour	0·90	59
3rd hour	0·89	78

X-ray of the renal tract was negative.

On October 25th cystoscopy was performed. A slight but definite obstruction to the passage of the cystoscope was felt about the position of the compressor. It was found impossible to wash the bladder quite clean, owing to the amount of pus collected in the dilated ureters and kidneys. The bladder was greatly trabeculated and sacculated, and the opening of the ureters were much dilated; no contractions of the ureters were seen. A small bougie was tied in the urethra with the idea of gradually emptying the bladder. Patient had a rigor the same night.

As the urethra quickly became intolerant of a bougie, a De Pezzer catheter was put into the bladder above the pubes on November 1st. The bladder was then washed out daily, the urine becoming considerably cleaner. When the bladder was washed out through the supra-pubic catheter a good stream of fluid passed through the urethra. On November 15th the urethra was examined through a special irrigating urethroscope, size No. 9 Charriére made by the Genito-Urinary company. It was found impossible to obtain a clear medium but a view was obtained of a greatly dilated and very inflamed posterior urethra. No fold or valve was seen but two openings of some size were seen in the floor of the urethra some distance on the distal side of the veru montanum. In spite of continued daily irrigation of the bladder the patient became uraemic and died on November 27th, 1928.

Only a partial post-mortem examination through the supra-pubic wound was permitted. All that was done was to remove the whole genito-urinary tract intact from kidneys to urethra. Both kidneys were soft, flabby, and bag-like. Ureters both dilated and thickened. Bladder greatly hypertrophied, with supra-pubic opening. Specimen hardened in formalin before further examination and therefore the figure shows much less than the actual dilatation (Fig. 4 and 5).

Further examination :—Bilateral hydronephrosis ; grossly dilated ureters. Ureteric orifices into bladder on the small side. Bladder very hypertrophied.

Urethra :—Veru montanum very big (size of small pea) and just in front of it appears to be a valve like obstruction—almost a double canal to the urethra about ¾-in. in length. In front of this again the urethra is dilated and shows signs of inflamation of its mucosa. Two openings which would admit a small probe were seen in the floor of the urethra and were thought to be the openings of the ducts from Cowper's glands.

The valve-like fold in the prostatic urethra can hardly have been the cause of the obstruction since the urethra was dilated for a considerable distance on the distal side of it, and it seems likely that the actual cause was a partial diaphragm distal to the compressor. This diaphragm was destroyed by the passage of the cystoscope. An obstruction in this situation would account for the paralysis of the compressor which allowed fluid to escape by the urethra while the bladder was being washed out through the supra-pubic opening.

Discussion.

Retention of urine in a child is usually due to phimosis, a pinhole meatus, some local inflammation, or sometimes to a calculus impacted in the urethra.

In the absence of one of these causes, the diagnosis of valvular obstruction can safely be made in any case where the signs are those of chronic retention and overflow, with a history dating back to infancy. There is always difficulty of micturition from birth, and the stream is very weak, or a mere dribble. Later continuous enuresis develops. In the more severe grades of obstruction the back pressure effects on the kidneys rapidly lead to a fatal result, as in the case recorded by King and Sheldon[7], but in cases showing the lesser degrees adult life may be reached. Usually the patient is brought for treatment during infancy or early childhood. On examination the child is found to be small and undeveloped for his age, generally pale and listless, often very thirsty, and showing signs of chronic uræmia. The bladder is distended and reaches up to the umbilicus or higher, urine is constantly dribbling from the penis, and the dilated ureters may sometimes be felt through the abdominal wall. The urine is of low specific gravity, contains a cloud of albumen and is always badly infected, usually with bacillus coli. Renal function tests will show diminished kidney activity. On the passage of an instrument through the urethra, the obstruction if due to a diaphragm (3rd type) may be recognized; but if due to a valve (1st or 2nd type), which will lie flat against the wall of the urethra, nothing abnormal will be felt. On cystoscopy the bladder shows signs of chronic cystitis and the usual evidence of back pressure in the form of trabeculation and sacculation. The openings of the ureters will be gaping to a greater or less degree and usually motionless.

The simplest method of treatment seems to be the retrograde passage of bougies, that is from the bladder towards the meatus, and in most cases this will probably effect a cure. Professor Young has invented a special punch by means of which he removes the valve after locating it with an urethroscope,

but the great degree of skill necessary to use such an instrument in the urethra of an infant must require an amount of practice that the ordinary surgeon is unlikely to obtain.

In the first case on which I operated (Case I) and passed bougies from the bladder, I think it doubtful whether I completely destroyed the valve, for the boy developed a supra-pubic fistula which did not heal until the bladder had been re-opened and bougies again passed. On account of this partial failure, in treating Case 2 I cut down on the urethra, and although I obtained a good view of the prostatic urethra I could see no valve. However the passage of bougies has cured the boy and he now passes an absolutely normal stream.

I have seen four patients with this condition within the last three years, and also two post mortem specimens, so that the condition cannot be so rare as is generally supposed. I remember on more than one occasion in the past having seen similar cases which were undiagnosed, and now that attention is being called to the condition I have no doubt that many more will be discovered before long.

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Fig. 2. (Case 1). Double pyelogram Nov., 1928. Pelves and calyces of both kidneys greatly dilated. Catheters curled up in largely distended ureters.

Fig. 3. (Case 2). Double pyelogram, April, 1929, showing slight degree of hydronephrosis and dilatation of ureters on both sides.

Fig. 4. (Case 3). Kidneys, bladder and urethra showing destruction of kidneys, dilatation of ureters, and great hypertrophy of bladder with dilatation of posterior part of urethra. The rod passes under a fold in the floor of the urethra.

Fig. 5. (Case 3). An enlarged view of part of the urethra and bladder in Fig. 4. The urethra was dilated as far as the distal end of the rod passing beneath the fold in the floor.

ACUTE SENSITIZATION IN AN INFANT TO COW'S MILK PROTEIN.

BY

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It has long been known that certain diseases such as asthma, eczema, urticaria and intestinal disturbances are often the result of an acute sensitization of the individual to certain foods, especially the protein part of the food. The majority of infants who are sensitive to proteins of various kinds have a family history of eczema, asthma or some similar disturbance and the case to be described, has a family history of these conditions and herself has eczema.

Even mild cases of hypersensitiveness to cow's milk are uncommon, but such an extreme example as the one reported here must be very rare and there are but few reports of such cases. Many are sensitive to cow's milk only, but the present case was equally sensitive to a large number of foods, including fresh and dried cow's milk, goat's milk, egg albumen, etc. Two such extreme cases are very clearly described by Tisdall and Erb[1].

By anaphylaxis is meant the development under certain conditions of a hypersensitiveness to foreign proteins, which may not be toxic in themselves. The term is applied to states of increased susceptibility to substances introduced into the body. If a minute dose of a foreign protein, such as horse serum, is given a patient and after an interval of not less than ten days a second larger dose is administered, grave symptoms of collapse associated with vomiting and diarrhœa may develop, and even death may occur in a small percentage of cases. It appears that the anaphylactic shock does not occur before the 10th day following sensitization, but once established it may last through life.

The nature of sensitization is not definitely known, but it is closely related to anaphylaxis. The chief difference is that to produce the latter condition experimentally in animals, it is necessary to give a preliminary injection of the foreign protein. The majority of cases who are sensitive to protein, show the typical reaction directly after the first injection of the offending protein, as happened in the case to be recorded[2]. It is likely that these cases simply inherit the tendency to become sensitized easily, and that some time before the comparatively large dose of protein is taken, minute sensitizing doses have been given. If so, the condition is identical with anaphylaxis.

Shannon[3] has shown that it is possible for minute quantities of protein to be absorbed and secreted essentially unchanged in the mother's milk, without producing any reaction in the mother, but when the mother's milk is ingested a definite reaction is produced due to the foreign protein.

Colic, vomiting, diarrhœa, repeated respiratory infections, and eczema in breast-fed babies are often the result of allergic reactions to food coming to the infant through the breast milk. Sensitization is often multiple and may be due to a majority of the foods in the mother's dietary. The repeated exacerbations

of eczema may be due to newly acquired sensitization to foods the mother eats. The manifestations of exudative diatheses are the result of anaphylactic reactions to food proteins in the mother's dietary, and not the result of fat intolerance in the majority of cases.

The case to be described developed eczema at the age of $3\frac{1}{2}$ months, possibly due to the foreign protein of the milk taken by the mother passing through into the human milk. It is curious to note that the baby gave a mild positive skin reaction to the mother's milk.

Symptoms. The symptoms of extreme hypersensitiveness are generally first noticed when an attempt is made to wean the infant and cow's milk is given. The symptoms arise directly the infant is given the cow's milk and they are most alarming and even dangerous. Within a few minutes of the infant taking the milk, he starts to cry and refuses to take the bottle. A minute or two later all the parts touched by the milk begin to swell, including the lips, tongue, mucous membrane of the mouth and œsophagus. If milk is spilt on the face the skin becomes red and swollen. The swelling in the mouth and pharynx causes difficulty in breathing and so endangers life from asphyxia. At the same time the infant becomes much shocked and in the event of recovery, he recovers in a short time though he is left much exhausted and upset for some hours.

Diagnosis. The diagnosis is unmistakable as the symptoms come on immediately after taking cow's milk in some form. The diagnosis is later confirmed by performing the skin test for cow's milk and other foods. A skin test is done by scarifying a small area of skin with a needle and placing on this area the milk or other food which is to be tested. If the test is positive, a red wheal will cover the site if the reaction is strong, while if the reaction is mild a redness only will appear. No change will take place with a negative reaction. By using the skin test, we can find which foods will cause trouble when given, and all foods should be tested carefully in this way, before they are given. Thus serious trouble is prevented before the infant is desensitized.

Treatment. The treatment of these cases consists in gradually desensitizing the patient to the peculiar kinds of foods to which he has an idiosyncrasy. It is a most difficult task and one that takes many months to bring about a cure in an extreme case.

Directly the condition is recognized it is essential that every effort should be made to continue the breast milk for a time, even though only a little is available. A wet nurse may be obtained, if the mother's milk has quite gone, to tide the infant over a few weeks.

The feeding of an infant, who cannot take cow's milk in any form, is most difficult, and it is hard to find an adequate diet to supply sufficient protein for the needs of a growing infant. Most of these infants, especially the severe cases, react to goat's milk in the same way as to cow's milk. If goat's milk is found to be suitable, it is most useful, though it is difficult to obtain in a hurry. Failing goat's milk, starchy foods such as groats or Benger's Food made with water, may be used and will supply the carbohydrate part of the food. Cod-liver oil emulsion can be used to supply the fat. It must be remembered

that cream will not do, as it comes from milk and will contain some protein, though some of the milder cases take it without harm. Banana and orange juice supply the fresh part of the food necessary. Fish made up in various ways is useful, and in the case to be described was a most useful form of diet, as the infant did not react to it.

The process of desensitization consists in giving minute doses of cow's milk at the start and gradually increasing the dose day by day. The increase of dose is governed by the ability of the infant to take the quantity of milk without developing any reaction. If a reaction such as urticaria, irritability, etc., is noticed, the dose must be kept the same for a time or even reduced for a day or two. In an extreme case it is wise to go slowly and not to hurry, as a setback is serious and prolongs the desensitizing time. Later on the rate of increase of the milk can be made more quickly. For the immediate treatment and relief of the acute symptoms a hypodermic injection of adrena'in (1–1,000) should be given. Brandy is also useful.

Case Report.

Baby, female, born 9th January, 1928.

Family History. On the paternal side, no history of eczema, asthma or food or drug idiosyncrasy. Mother had eczema as a child until the age of 10 years; uncle had eczema and hay fever; grandmother had asthma and was also very sensitive to strong sunlight.

Pregnancy was uneventful. Birth weight, 7 lb., and she was well developed and healthy. Breast feeding started at once and continued without event up to 9 months. Baby gained weight steadily though rather slowly. Vaccinated at the age of 3 weeks and a week later became cross and rather more upset than is usual.

At the age of 3½ months started with eczema on the scalp which spread to the face and body. The usual treatment was adopted and the eczema improved only to return again after a few days and persist. At the age of a few weeks old, the baby had one small feed of diluted cow's milk without any ill effects. Apart from this she had no food other than breast milk, except a little orange juice and Virol at times, until weaning was attempted at the age of 9 months.

Weight at 9 months was 13 lb. 1 oz. For the description of the immediate subsequent events after the infant was given cow's milk, I am indebted to the father, who is a medical man. At the age of 9 months it was decided to wean the baby and a milk and water mixture was given with a spoon. Almost immediately the upper lip began to swell and it was thought that she had bitten her lip. The feed was continued although the baby cried vigorously and resented the feed strongly. A bottle was then tried. In all little over 1 oz. of the mixture was given in 10–15 minutes. Acute illness set in almost at once. The baby was then noticed to have marked œdema of the face, especially of the lips, which were more than twice their normal size and completely everted. There seemed to be much difficulty in swallowing due to swelling of the tongue and possibly also of the œsophagus. The skin became red where the milk had been spilt on the face in the endeavour to feed the baby at the start. She could not vomit at this time because of the swelling in the mouth and pharynx. She then appeared very distressed, pale, and cyanosed. Dyspnœa with rapid breathing was marked. As soon as the swelling subsided about 4 hours later, she vomited curdled milk mixed with mucus and also spat up some blood. Brandy was given during the acute attack and helped to revive her. Only boiled water was given for the rest of the day and during the night. By the next morning the œdema of the face and

lips had quite disappeared, but she appeared pale and somewhat distressed. Small feeds from the breast were started again and by the evening she appeared quite normal. During the day she passed a motion containing much curd, mucus and clots of black blood.

As the result of what had taken place it was evident that the baby was extremely sensitive to cow's milk, and that she had had a severe anaphylactic shock. The baby was 9 months old and it was imperative to start with food to supplement the breast milk which could not be expected to last long or at any rate to be sufficient. Since cow's milk is such a staple article of food during infancy and childhood, it was evident that she could not go through life without it and that it was necessary to desensitize her as soon as possible. It was then decided to try a weak dried milk mixture (Cow & Gate) very gradually in small doses. A teaspoonful of this mixture was given and in 5 minutes a second teaspoonful. The lips then began to swell and the face to be œdematous. The feed was stopped at once and she appeared to be only slightly distressed. Two hours later she began to wheeze, and passed a curdy motion as before. Accurate daily records were then kept and the exact diet recorded. It was evident that the correct line of treatment was to try to desensitize her to cow's milk, as she could not possibly grow up without it. Various skin tests were then done at intervals with different foods, and no food was ever given unless the skin test was negative. Cow's milk gave the following reaction—after 5 minutes there appeared an urticarial blotch larger than a penny and the swelling extended over the area of skin where the milk had been placed. The swelling over the scarified area remained until the evening. Cumming[4] describes such a case.

White of egg gave an even more marked reaction than the cow's milk and an urticarial rash came on the abdomen and groins and thighs. The rash lasted half an hour and then faded.

It became evident that she was no ordinary case of cow's milk hypersensitization but that she was sensitive to other foods as well.

The desensitization to milk was then started in the following manner. One drop of milk measured with a hypodermic syringe, in 4 ozs. of water was used as the stock solution and one teaspoonful of this mixture was given 3 times a day, making ·03 min. of milk to a feed or ·09 min. per day. Even after this small dose of cow's milk it was noticed that a slight urticarial rash appeared on the neck and under the chin 20 minutes after giving the milk mixture. This rash disappeared in 10 minutes. She also became irritable. There were no general symptoms. From this it was clear that the infant reacted to the minutest quantity of cow's milk and that desensitization must go on very slowly at any rate at the beginning.

The diet, then, consisted of 3 breast feeds, with two of groats made with water, together with the milk mixture. She also had a small teaspoonful of cod-liver oil emulsion 3 times a day, and orange juice. The milk mixture was gradually increased by adding an extra drop of milk to the 4 oz. of water each day. Any attempt to strengthen the milk mixture too quickly gave rise to an increase of the eczema, irritability, asthma and vomiting of mucus. By the end of the first month just over 13 min. of actual milk was being taken without reaction. She weighed 13 lb. 15 oz., an increase of 14 oz. in the month, showing that she was getting enough food. Further skin tests were then done, so as to add to the dietary. The following articles gave no reaction.

(1) Yolk of Egg.
(2) Banana and stewed apple.
(3) Fish.
(4) Farola.
(5) Chocolate.
(6) Potato.
(7) Biscuit.
(8) Butter.

The following, in addition to the milk, gave a positive reaction.

(1) White of egg (very marked)
(2) Soup made from beef, tomato and carrot.
(3) Whey.
(4) Malt.
(5) Virol.
(6) Breast milk gave a slight reaction. It is probable that the eczema, which started at $4\frac{1}{2}$ months was caused by the breast milk.

The diet was then increased by those foods which gave negative reactions. The yolk of egg was obtained by hard boiling the egg so as to 'set' the white. The eczema still continued to trouble her, showing that she was having a reaction to the food. She was also inclined to wheeze and cough a good deal at times. By the end of the second month she was having nearly a teaspoonful of milk a day and it was possible to increase the milk by 2½ min. a day. Fish was a great help in the dietary as she took it well. By the end of the third month she was having just over two teaspoonsful of milk daily.

At this time she had a marked setback probably due to very cold weather and to the fact that the cows were fed in a different manner. Dried milk was then substituted for the fresh milk and all went well again. By the end of the fourth month 1 oz. of milk a day was taken. By the end of the fifth month she was having 2 oz. of milk a day, with an increase of a teaspoonful daily. By the end of the sixth month, age 15½ months, she was having 10 oz. of milk a day. Her weight was then 16 lb. There was no eczema and she had cut ten teeth. From the various skin tests it is obvious that the child will have to be desensitized to malt, etc. This should be an easier and quicker task than the cow's milk. It is also clear that as she grows up a careful watch will have to be kept on her diet, especially when new foods are tried, and the skin tests will be most helpful.

Great precautions will have to be taken also before she is given any serum or antitoxin and a small preliminary dose must be tried before the necessary quantity is injected.

Adrenalin should be available at all times.

During the time that the mother was breast feeding this baby, she was taking Ovaltine regularly. Ovaltine contains malt, egg and milk, all of which give a marked positive skin test on this baby. It is likely that the baby's eczema was at least aggravated by the Ovaltine, which was secreted in the breast milk.

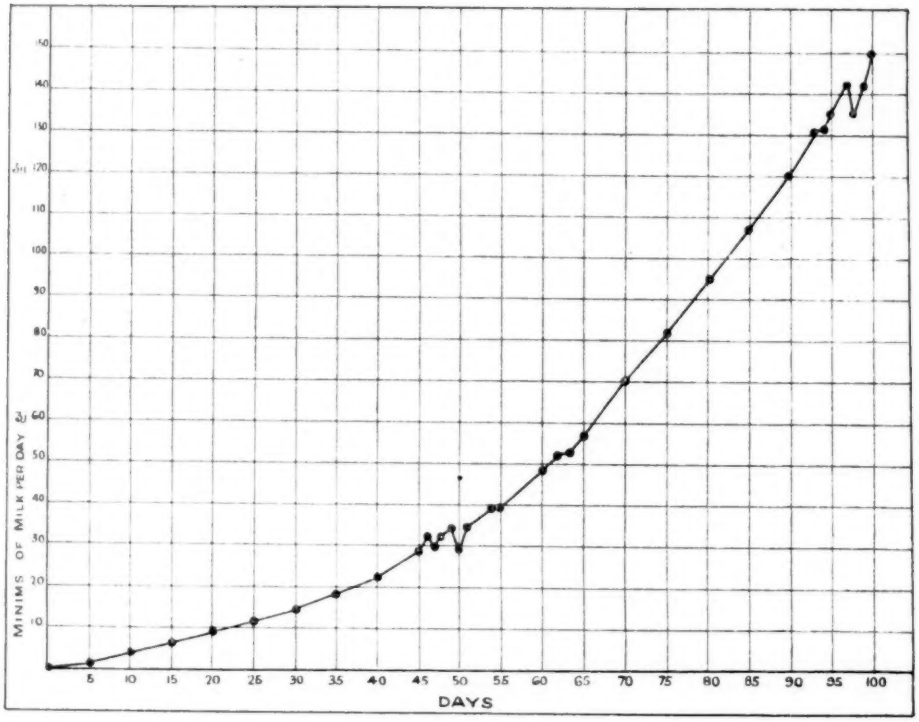
The baby, who is now eighteen months old and is well in every way, except that she is under weight (17½ lb.) and rather thin. She has 16 teeth and is bright and active. She is having 20 oz. of whole milk a day and a good varied diet, which she takes well.

The skin test for milk is still mildly positive, but gives a far less marked reaction than it did at the beginning. Egg white gives a fairly strong reaction still and she is now being desensitized to this food in the same way as was done with milk.

TABLE SHOWING SUMMARY OF SKIN TESTS.

Positive.	*Negative.*
Cow's milk ++++	Benger's Food.
Dried Milk ++++	Robinson's Groats. Farola.
Goat's Milk ++++	Cod liver oil; Scott's Emulsion.
White of Egg ++++	Barley.
Whey +++	Butter.
Ostelin ++	Banana.
Osteomalt ++	Fish (plaice, halibut, etc.)
Soup ++	Potato.
Virol ++	Apple juice, orange, pear, prunes.
Malt +++	Honey.
Tomato ++	Carrot, sprouts, etc.
Breast Milk +	Chicken.
Mutton Broth +	Bacon "dip."
Veal „ +	Biscuits.
Marmite ++	Yolk of egg.
Golden Syrup +	Chocolate.

CHART SHOWING RATE OF INCREASE IN THE AMOUNT OF MILK GIVEN DAILY.



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STUDIES OF PNEUMONIA IN CHILDHOOD.

V. EMPYEMA.

BY

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Clinical Considerations.

Incidence. In our clinical series of 648 cases of pneumonia in children from birth to twelve years, analysed in the first of these studies[1], empyema occurred in 89, giving a frequency of 1 in 7. This approximates closely to the incidence of 1 in 8 in Spence's series of 204 cases of empyema from the Babies' Hospital, New York[2], and of 1 in 9 of Dunlop's 98 cases[3]. Our definition of empyema was the existence of pus or sero-purulent fluid in the pleura, even in small amount, determined either during life or after death : the same standard was adopted by Spence. In our cases, the incidence was lower in the earlier age periods and was appreciably higher in later childhood. Thus, in the periods from birth to two years and from two to five years, it was almost equal—1 in 10 ; while from five to twelve years, it was 1 in 5. There were 3 examples of well-marked pyo-pneumo-thorax in the series.

Mortality. For the total, the mortality was 40·5 per cent. For the age periods already given, it was as shown in Table 1.

TABLE I. (Clinical).

Age period	Death rate
Birth to 2 years ...	75 per cent.
2 to 5 years	31·5 per cent.
5 to 12 years	8·5 per cent.

Sex. There were 53 boys and 36 girls in the group, figures which correspond closely to the 124 boys and 80 girls in Spence's series, and also to the general preponderance of boys over girls in our inclusive group of all types of pneumonia.

Site. The right pleura was involved in 35 and the left in 47 cases. The percentage of deaths was higher in the right-sided (16 deaths) than in the left-sided group (16 deaths). Of 7 bilateral cases, 3 recovered. In the great majority of cases, the empyema was basal. In 4 it was localized about the

middle of the parietal pleura: all these recovered, 3 after single or repeated aspiration without further drainage. A brief record of one of these cases follows:—

CASE I. Male, aged 8 years. Pneumonia 3 weeks before admission. Crisis after 2 weeks' acute illness, followed by relapse. On admission, percussion dullness limited to a considerable area in right axilla. X-ray photograph (Fig. 1) showed a large circular shadow on the right side, with luminous lung above and below. The first two explorations were negative; a third in the 3rd interspace aspirated 5 ounces of thick pneumococcal pus. Steady uninterrupted convalescence followed. It is possible that this empyema was interlobar: if so, it is the only example of an interlobar collection in the clinical series.

Type of pneumonia. The antecedent pneumonic illness was alveolar (lobar) in type in 45 cases, with 6 deaths: broncho-pneumonic in 13 cases, with 13 deaths: and undetermined in 31 cases, with 17 deaths.

Syn-pneumonic and meta-pneumonic empyema. In a study of 52 cases of empyema in children under 2 years of age, Cameron[4] introduced this classification. The prognosis depends to a large extent on the presence or absence of active pneumonia at the time of development of the empyema, the high death-rate in syn-pneumonic empyema being due to the extent and severity of the underlying pneumonia. This difference in prognosis is most evident in the first two years, but in later years the death-rate in syn-pneumonic empyema is still appreciably higher than in the meta-pneumonic or residual type. It has been found possible to classify 86 of our 89 cases on this basis, and the results (Table II) generally confirm the value of the classification as a guide to prognosis.

TABLE II. (CLINICAL.)

Age period	Syn-pneumonic		Meta-pneumonic	
	Total	Deaths	Total	Deaths
Birth to 2 years	27	25	8	1
2 to 5 years	4	2	14	3
5 to 12 years	11	3	22	0
Total	42	30	44	4

Bacteriology. This was recorded in 70 of the 89 cases (Table III).

TABLE III. (CLINICAL.)

Micro-organism	Total	Deaths
Pneumococcus	53	18
Streptococcus	7	3
Staphylococcus	2	2
Mixed	8	6

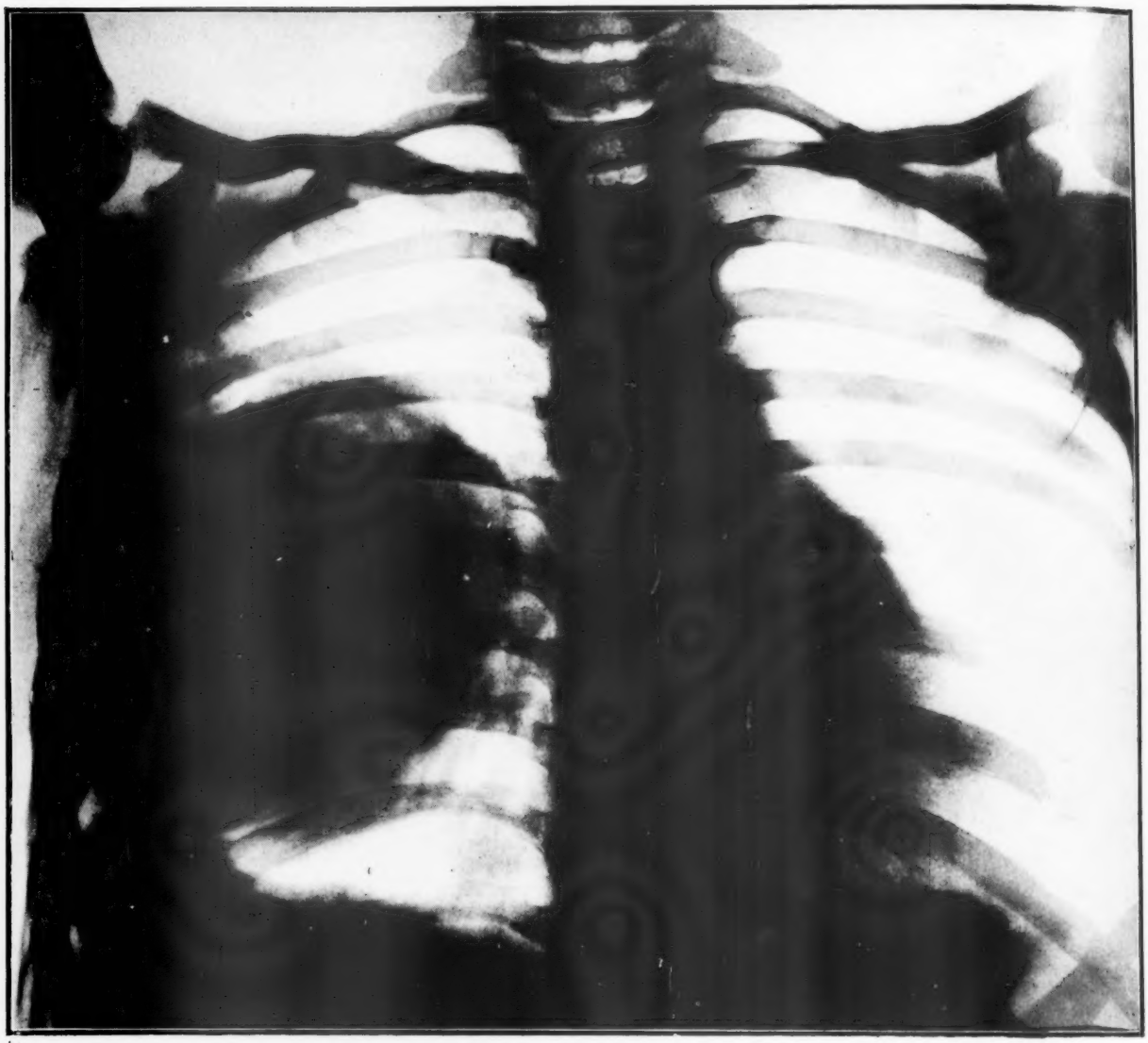

FIG. 1. Radiograph of interlobar empyema (Case I).

PATHOLOGICAL STUDY.

Among the total of 244 post-mortem cases of pneumonia in children analysed in our first study, there were 69 of empyema, giving a frequency of almost 27 per cent.

Site and extent of empyema cavities. The right side only was affected in 25 cases; the left in 25; 19 were bilateral. In 27 empyemata, organized adhesions were absent and the whole sac was involved. In 33 instances, organized adhesions obliterated part of the pleural cavity and the pus was shut off in circumscribed pockets of varying size. In the remainder the empyema occupied the greater part of the pleural sac, but limited adhesions were present.

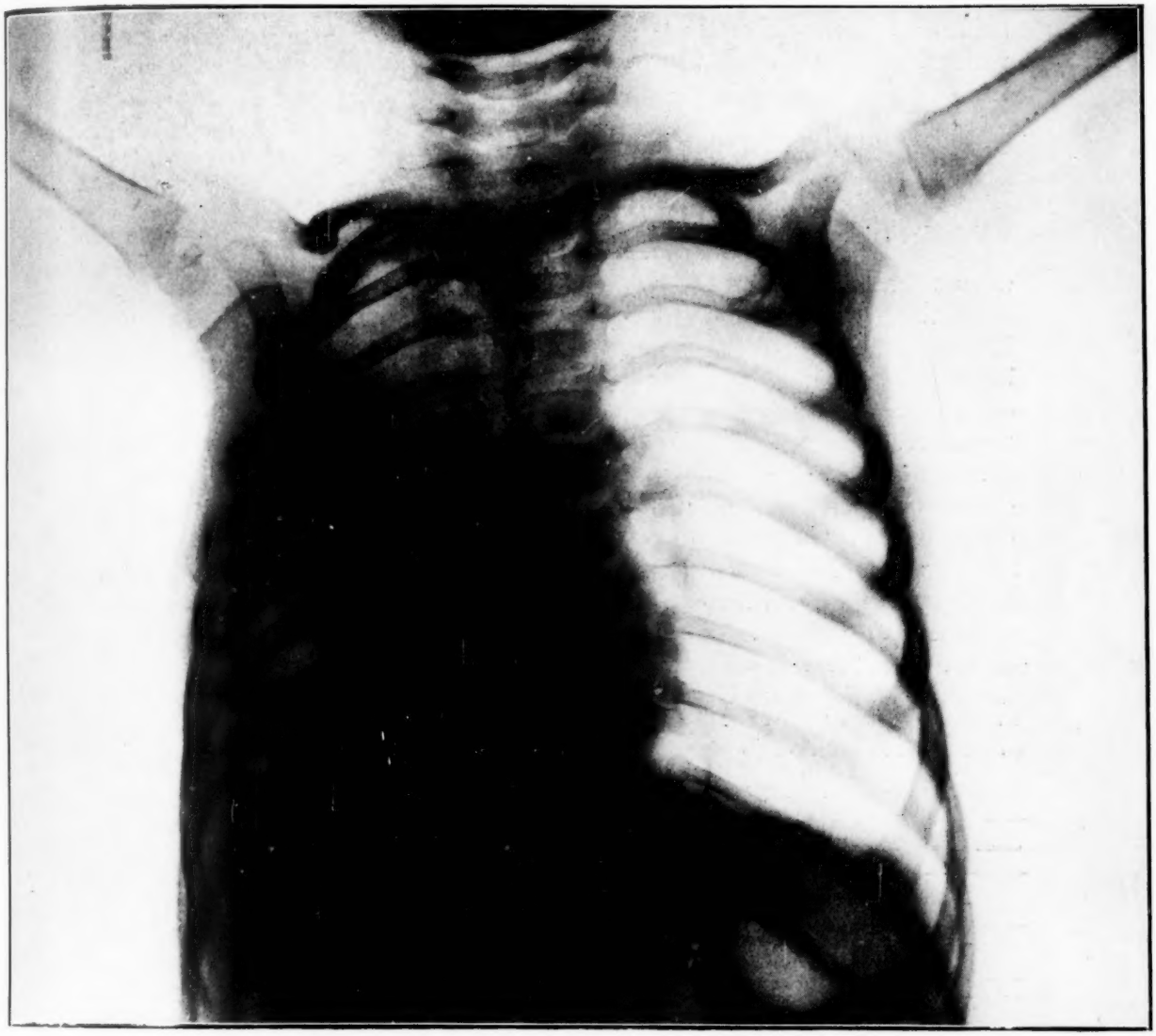

FIG. 2. Radiograph of right-sided empyema and collapsed right lung (Case III. See also Figs. 5 and 6). Note displacement of heart towards side of empyema.

Where organized adhesions are present, the pus may collect in several separate pockets in one pleural cavity. In 8 of our 33 cases two such independent collections were found; in one case there were three pockets separated from each other by firm fibrous adhesions.

The sites of the localized collections of pus may be of some interest. The most usual position was at the base (19 cases, of which 6 involved the diaphragmatic surface, most of the rest being posterior). In only one case was the pus entirely confined to the space between the inferior surface of the lung and the diaphragm. In 8 cases collections of pus were found in the region of the apex, 3 of them being situated on the medial aspect. In 3 cases the

pockets were on the mediastinal surface near the root : in 7, on the anterior surface ; and in 6 on the posterior. In 2 cases interlobar collections were found, but in only one of these was the pus entirely imprisoned between the lobes.

Character of the empyema fluid. In the localized empyemata with fibrous adhesions, the fluid was usually of the nature of thick pus. Where adhesions were absent and the whole sac was involved, it was more usual to find thin pus or sero-purulent fluid, with masses of thick fibrin floating in it or adhering to the pleural surfaces. The amount of this thick fibrinous exudate was often very great.

Types of associated pneumonia. In 58 of the 69 cases, pneumonia of some kind was present in the lungs at the time of death : in 11 no pneumonia could be detected at autopsy. In 45 cases it was possible to determine the type of the pneumonia ; in 13 this was not possible, because only remnants of pneumonia were present, and these cases were placed in a group termed 'unclassified.' Table IV shows the types of pneumonia in which empyema occurred, the number of cases of empyema associated with each type, and, for comparison, the total number of cases of each of these types in our whole series.

It will be noted that the incidence of empyema was somewhat higher relatively in alveolar than in broncho-pneumonia. But at the same time it is important to remark that almost exactly one-half of the empyemata in this series occurred in cases of broncho-pneumonia. We find it, therefore, impossible to agree with the view which has been expressed, that empyema seldom occurs in broncho-pneumonia. Our experience is that the great majority of fatal cases of empyema in children under two years of age complicate broncho-pneumonia (see Fig. 3, 4, 5 and 6).

TABLE IV. (Post-mortem.)

Type of pneumonia	Total	Empyema	Per cent. Empyema
Broncho-pneumonia	140	34	24
Alveolar (lobar) pneumonia	23	8	35
Septic (pyæmic) pneumonia	4	1	25
Chronic pneumonia (bronchiectasis)	5	2	40
Unclassified	17	13	70
No pneumonia	—	11	—

Age incidence. All the children were under 8 years of age ; 47 were under two years. The largest number (31 cases) was found between the sixth and eighteenth months. The high incidence of fatal cases in the first two years is explained, as has already been stated, by the deadly character of the accompanying pneumonia during that age period.

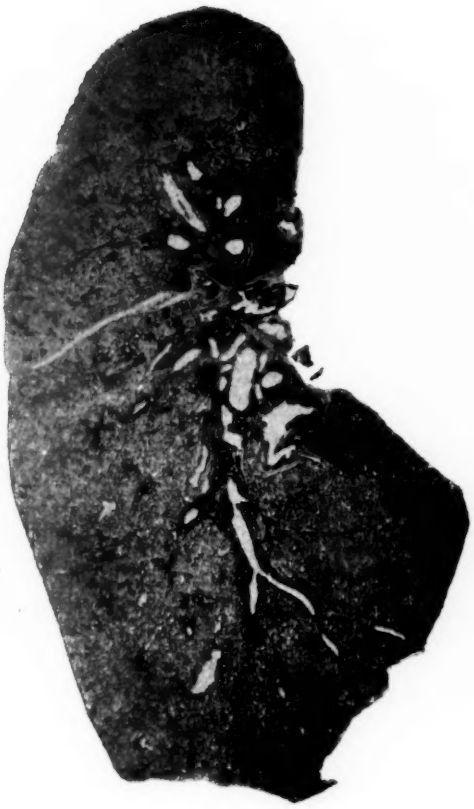

FIG. 3. Same as Fig. 4. Right lung. Capillary bronchitis and acute broncho-pneumonia through out, with confluence along medial border.

FIG. 4. Girl aged 1 year and 9 months (Case II). Left lung. Empyema of 3 weeks' duration. Organizing exudate over entire pleural surface; sub-pleural abscess (A) on diaphragmatic surface; broncho-pneumonia and collapse throughout lung.

FIG. 5. Girl aged 9 months (Case III). Right lung. Empyema of 5½ weeks' duration. Fibrous thickening of pleura on lateral surface; large sub-pleural abscess (A) about to rupture at base; deep-seated abscess (B) in lower lobe; almost complete collapse of lung.

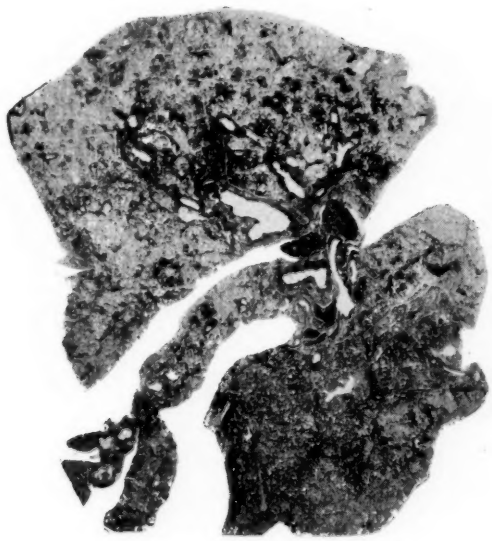

FIG. 6. Same case as Fig. 5. Left lung. Acute broncho-pneumonia, especially in lower lobe. Well-marked acute vesicular emphysema. (The tri-lobed appearance of this lung is an artefact.)

Sex. There were 42 boys and 27 girls in this series.

Complications accompanying empyema. A fairly large proportion of the empyema cases showed other grave complications of pneumonia. The chief of these were pericarditis, peritonitis and meningitis. In 21 of the 69 cases of empyema, one or more of these three conditions occurred. Their frequency was :—Pericarditis, 16 : peritonitis, 7 : meningitis, 2. For comparison, the frequency of these complications in the 175 cases of pneumonia without empyema in our series was :—pericarditis, 2 : peritonitis, 3 : meningitis, 4. These figures show that in this series both pericarditis and peritonitis occurred much more frequently in cases of empyema than in pneumonia without empyema, but that this was not the case with meningitis. Pericarditis was present in 23·2 per cent. of the cases of empyema, compared with 1·1 per cent. of the cases of pneumonia without empyema : the corresponding figures for peritonitis were 10·1 per cent. compared with 1·7 per cent. : while for meningitis they were 3 per cent. compared with 2·2 per cent.

These facts may have some bearing on the question of the channel by which the infection spreads to these various secondary sites. In the case of meningitis there can be little doubt that the usual route by which the infection reaches the meninges is the blood stream. In the case of pericarditis and peritonitis there is a possibility of a more local spread, probably by lymphatics : but the view that these also are results of a blood-spread infection is widely favoured. The figures just presented would seem to support the view that pericarditis and peritonitis may be often—perhaps most often—the result of spread of infection by the more direct route, and not of a blood infection. It is always dangerous to draw conclusions from small numbers of cases, and it must be admitted that there is a greater probability of blood infection in cases of pneumonia complicated by empyema, because they are on the average more severe and prolonged, and run a greater risk of the development of a secondary septicæmia. Yet if all these three conditions were alike caused by blood infection, it might be expected that the incidence of all three would be similarly affected by the occurrence of empyema.

Suppuration in the lungs. Suppuration or necrosis in the lungs was found in 26 of the 69 cases of empyema (37·7 per cent.). Seventeen of these were cases of broncho-pneumonia, while only one was alveolar (lobar) pneumonia. Exactly one-half of the cases of broncho-pneumonia with empyema showed suppuration or septic necrosis in the lungs. In a few instances where suppuration was present, it could be shown at autopsy that an abscess or abscesses in the lung had burst into the pleural sac, and had thus, in all likelihood, caused the empyema. In several other instances abscesses, as yet unruptured, projected immediately beneath a stretched, infected and sometimes necrotic pleural membrane (Figs. 4 and 5). Sometimes the abscesses were deep-seated, and had no apparent connection with the empyema.

In the 175 cases of pneumonia without empyema, suppuration or necrosis was found in 21 (12 per cent.). From this it would appear that these changes in the lungs are distinctly more common in cases of empyema than in pneumonia without that complication. While in some instances it is fairly obvious that

the suppuration in the lung is the direct cause of the empyema, in others it is no easy task to determine which of the two conditions arose first. For while it is evident that suppuration in the lung renders empyema more likely, it is probable that the converse is true also, that the presence of an empyema increases the risk of suppuration in the lung. The reason for this is as follows. Suppuration in the lungs in cases of the kind being considered is usually in the form either of bronchial abscesses or of septic infarcts (Fig. 9). Brief mention of this was made in the third of these studies[5], when it was pointed out that bronchial abscesses are the result of suppuration starting in the bronchial walls and peribronchial lymphatics ; and septic infarcts the result of thrombosis of blood vessels due to involvement of their walls in a suppurative inflammation

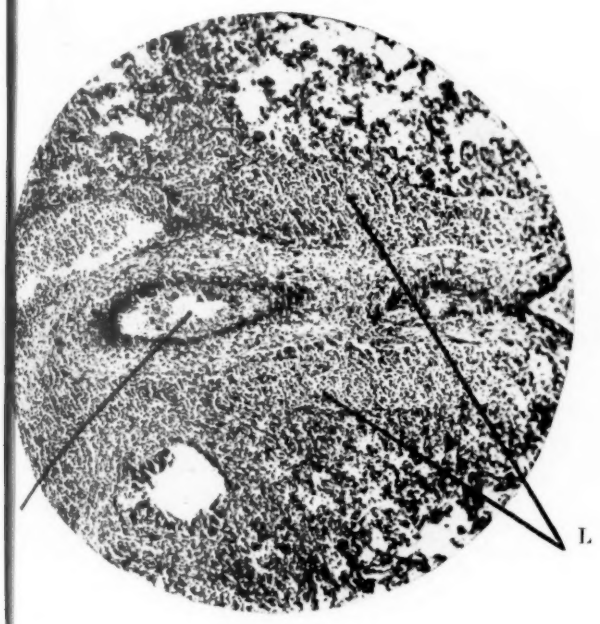

Fig. 7. Suppuration in perivascular lymphatics. Boy aged weeks (Case IV). (A) Artery. (L) Lymphatics distended with pus.

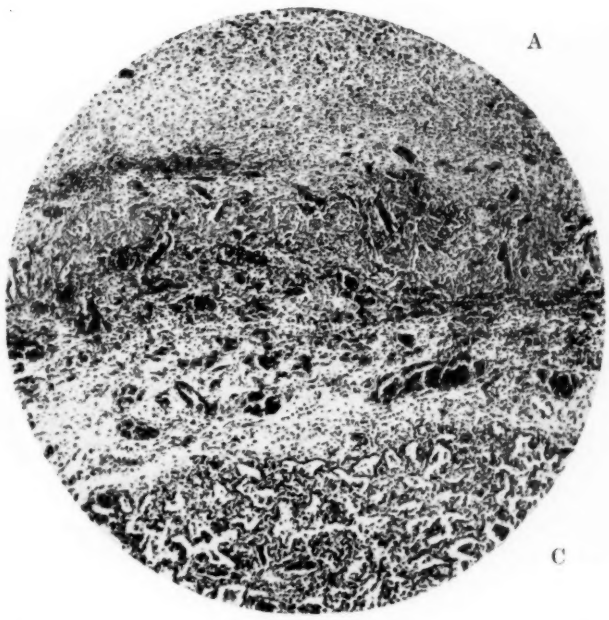

Fig. 8. Same case as Fig. 4. To show the amount of pleural thickening after a period of not more than 3 weeks. (A) Fibrino-cellular exudate. (B) Thickened pleura with exudate in process of organization. (C) Lung.

spreading along the perivascular lymphatics (Fig. 7). It is probable that the impairment of circulation of blood and lymph, and the restricted movement of the lung in the presence of an empyema, favour the development and spread of this suppurative lymphangitis, with its grave effects upon the lung.

Fibrosis of the pleura and lung. A certain amount of fibrous thickening of the pleura is probably inevitable in most cases of empyema which survive long enough to allow it to occur. Even when the pus has been successfully evacuated, a quantity of thick fibrino-purulent exudate often remains adhering to the pleural surfaces. Organization of this is bound to lead to the formation of new fibrous tissue, and probably to the production of adhesions (Fig. 10).

It is remarkable with what rapidity a fairly thick layer of new fibrous tissue may form beneath an inflammatory exudate. Even after two or three weeks its amount may be quite considerable (Fig. 8).

In cases of longer standing, especially when the lung has remained for some time in a partly collapsed condition, there may be extensive fibrosis of the lung itself. The beginning of this may be found a few weeks after the onset of empyema, in the form of fibrous tissue proliferation in the interlobular septa, commencing at their junction with the pleura and spreading inward (Fig. 11); and also in the walls of alveoli immediately beneath the pleura or

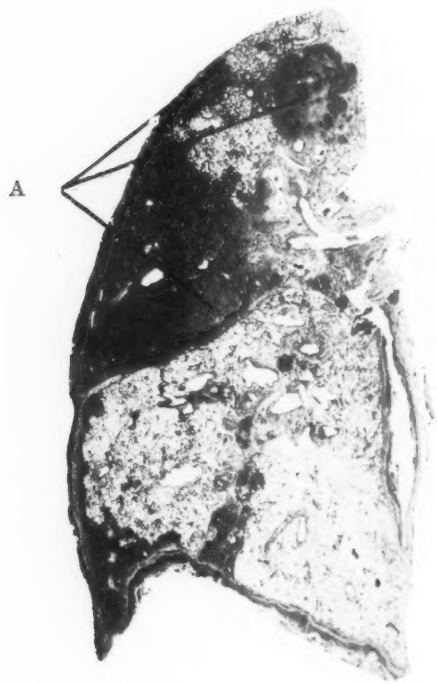

FIG. 9. Boy aged 1 year and 2 months (Case V). Right lung. Empyema of 3 weeks' duration. Organizing exudate in pleura over lower lobe; partial collapse of lung at base; multiple areas of infarction (A) and of pneumonic consolidation in upper lobe.

adjacent to thickened septa. In more advanced cases this chronic interstitial pneumonia may lead to an almost complete obliteration of the air-containing lung tissue. Interlobular septa, enormously broadened by the growth of new fibrous tissue in them, pass in from a greatly thickened pleura and divide the lung substance into widely separated lobules, in which the alveoli are more or less completely collapsed and show a variable amount of fibrous thickening of their walls. Fibrosis of the alveolar walls is, however, sometimes less striking than might be expected. The constant outstanding feature of pleurogenic fibrosis of the lung would appear to be the immense thickening of the septa which, together with the thickened pleura, effectively prevents the normal expansion of the lung.

ABSTRACTS OF CASES ILLUSTRATED.

CASE II (Fig. 3, 4 and 8). *Left-sided empyema, complicating acute broncho pneumonia.* Female, aged 1 year and 9 months. Died 3 weeks after onset of illness, and 3 days after admission to hospital. Pus (pneumococcal) removed by syringe from left pleura on day before and day after admission. On *post-mortem* examination, large quantity of thick yellow pus in left pleural sac; whole pleura covered with thick fibrino-purulent exudate with exception of medial surface where loose adhesions were present. Left lung collapsed and airless; several small abscesses in lower lobe, one immediately under pleura and in relation to empyema cavity. Right pleura healthy. Right lung emphysematous, with recent acute broncho-pneumonia; strip of consolidation along medial border. Tracheo-bronchial glands swollen and soft. *Microscopically*, degree of organization and formation of young fibrous tissue in left visceral pleura surprisingly

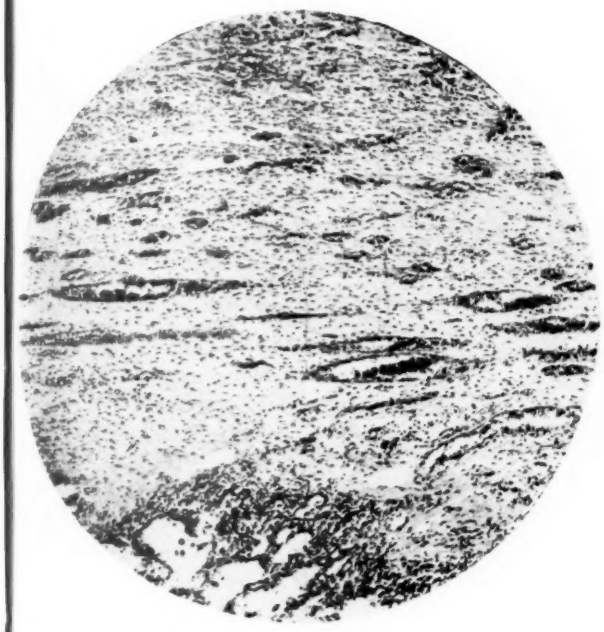

FIG. 10. Pleura from empyema of about 10 week's duration. Girl aged 1 year and 5 months (Case VI). To show thickening of pleura with well-formed vascular fibrous tissue.

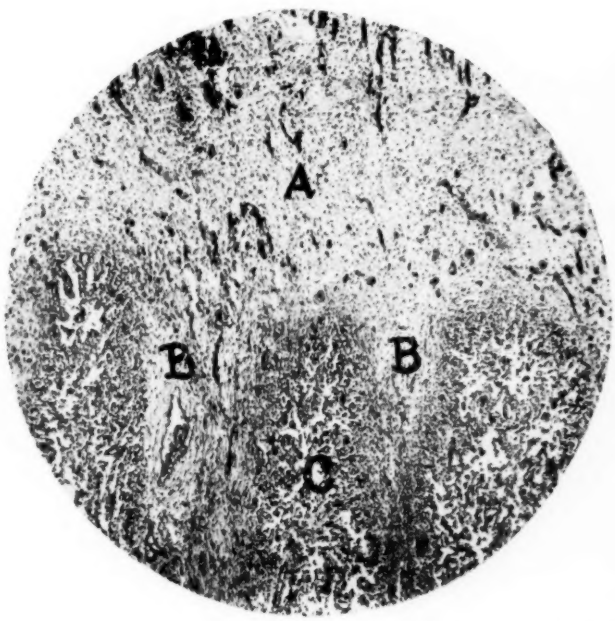

FIG. 11. To illustrate pleurogenic fibrosis. Empyema said to be of 6 weeks' duration. Boy aged 1 year and 8 months (Case VII). (A) Pleura with increase of fibrous tissue. (B) Thickened interlobular septa. (C) Collapsed lung.

advanced for an inflammation of 3 weeks' duration; marked bronchitis in left lung, suppurative in lower lobe; several small abscesses of bronchial origin in infero-medial portion; combination of collapse and consolidation in lung substance.

CASE III, (Fig. 2, 5 and 6). *Right-sided empyema, complicating broncho-pneumonia.* Female, aged 9 months. Died some 5½ weeks after onset of illness and 10 days after admission to hospital. Pus (pneumococcal) removed by syringe on two occasions while in hospital. X-ray photograph (Fig. 2), taken on day before death, of considerable interest because of displacement of heart to affected side. On *post-mortem* examination, more than half a pint of greenish-yellow pus in large pocket on lateral aspect of right lung; remainder of pleural sac obliterated by recently organized adhesions. Right lung collapsed and compressed against mediastinal tissues; projecting sub-pleural abscess on infero-medial aspect; smaller abscess in substance of lower lobe. Left pleura healthy. Left lung very markedly emphysematous, almost completely over-lapping

heart; bronchitis and small areas of broncho-pneumonia present, especially in lower lobe. *Microscopically*, great thickening of right pleura in relation to empyema cavity seen to be due mainly to well-advanced organization. Bronchi throughout right lung inflamed, with thick cellular walls denuded of lining epithelium; abscess in substance of lower lobe, referred to above, obviously of bronchial origin; solid condition of right lung due largely to collapse, but very definite broncho-pneumonic element also evident.

The displacement of the heart to the affected side in this case, illustrated in the X-ray photograph, must be ascribed, in part at any rate, to the push of the markedly emphysematous functioning left lung. There is no question of its being the result of traction by a fibrosed right lung, as the illness was too short to allow of the necessary degree of fibrosis, and, in any case, microscopic examination effectually rules out the possibility. It is of interest in connection with the recent observations of Tallermann and Jupe[6].

Case IV, (Fig. 7). *Fulminating pneumonia, of septic type, with early empyema.* Boy, aged one month; twin; full-time; breast-fed. Illness said to have been of only 36 hours' duration; convulsions the most prominent feature. On *post-mortem* examination, about an ounce of turbid blood-stained fluid in right pleura. Right lower lobe solid and of a deep red colour, with certain areas in process of undergoing softening. Left pleura inflamed in patches but without any fluid content. Left lower lobe less completely consolidated than right, but also hæmorrhagic and the site of breaking-down pneumonic areas. *Microscopically*, essential condition seen to be broncho-pneumonia of a very acute septic type, but consolidation contributed to by hæmorrhage and necrosis; suppurative lymphangitis a prominent feature.

Case V, (Fig. 9). *Right-sided empyema, complicating pneumonia with septic infarction.* Male, aged 1 year and 2 months. Died 3½ weeks after onset of illness and 12 days after admission to hospital. Clinically, regarded as case of lobar pneumonia, at first of right upper and later of left lower lobe. Cerebral symptoms prominent. Empyema (pneumococcal) detected on right side 6 days after admission, *i.e.*, 2½ weeks after beginning of illness; treated by repeated aspiration. On *post-mortem* examination, not much pus, but very thick fibrino-purulent exudate in lower part of right pleural sac. Right upper lobe extensively consolidated, as a result partly of pneumonia and partly of necrosis; several independent areas of latter, some of them becoming purulent. Small abscesses also present in middle lobe. Mixture of pneumonia and collapse in infero-lateral part of right lower lobe. Left pleura acutely inflamed over lower lobe: no free fluid. Large patch of pneumonia of alveolar type in left lower lobe. *Microscopically*, commencing organization of copious pleural exudate on right side; type of pneumonia in right upper lobe difficult of definition, as septic infarction so widespread. Necrosis regarded as having developed in pneumonic lung as a result of infection of vessel walls from perivascular tissues, and consequent thrombosis.

Case VI, (Fig. 10). *Long-standing left-sided empyema.* Female, aged 1 year and a half. Illness of about 11 weeks' duration. Main incidence of pneumonia said to be at first in right lung, later in left. Admitted 3 weeks after onset of symptoms, with left-sided empyema (pneumococcal). Treated by repeated aspiration and then by drainage through cannula inserted between ribs. Progress fairly satisfactory for some weeks. Severe constitutional symptoms and jaundice before death. On *post-mortem* examination, left pleural sac largely obliterated by dense organized adhesions; drainage opening communicating with relatively small unobliterated pocket; abscess in chest wall in relation to drainage opening. Left lung much collapsed; remnants of broncho-pneumonic process in substance; bronchi slightly dilated and filled with pus. Recent acute pleurisy with effusion on right side. Small scattered patches of consolidation and softening in right lung, more suggestive of blood-borne than air-passage infection. Profound toxic changes in organs, especially liver. Death regarded as result of terminal septicæmia.

Case VII (Fig. 11). *Left-sided empyema: original pneumonia probably broncho-pneumonia.* Male, aged 1 year and 8 months. Died after an illness which, so far as could be ascertained, lasted about 6 weeks. Admitted 3 weeks after onset. Empyema suspected but not discovered till a week later; aspirated on two occasions and then drained by rib-resection. Cavity not large and drainage apparently complete. Constitutional disturbance continued, however, and death occurred about a week after operation. On *post-mortem* examination, left pleural sac obliterated by dense fibrous adhesions except at point of drainage, where small empty cavity

remained. Left lung partially collapsed, but not pneumonic. Right pleura acutely inflamed. No pneumonia obvious in right lung. Early acute pericarditis and peritonitis. Pronounced toxic changes in organs. *Microscopically*, right pleura greatly thickened by well-organized fibrous tissue; interlobular septa in relation to pleura also markedly thickened. Intervening lung substance collapsed. Surprising degree of fibrosis in pleura and stroma of lung, for inflammation of 6 weeks' duration. Death, as in last case, due to septicæmia.

Summary.

A short survey of 89 clinical and 69 post-mortem cases of empyema in children is presented. Figures are given showing age incidence, mortality, associated types of pneumonia, and frequency and situation of localised collections of pus. The association of empyema with lung abscess, pulmonary fibrosis, and certain other complications is briefly discussed.

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Acknowledgments.

In connection with this series of studies of pneumonia and its complications in childhood, we wish to express our indebtedness to :—The Committee of the Laboratory of the Royal College of Physicians, Edinburgh ; Lieut.-Col. A. G. McKendrick, superintendent of the Laboratory ; the late Dr. J. W. Dawson and Lieut.-Col. W. F. Harvey, in whose department most of the technical work was carried out ; Mr. T. D. Hamilton, who prepared the very beautiful large sections with which we worked, and who was also responsible for the photographs ; Dr. Norman Carmichael and Dr. Lewis Thatcher, for permission to refer to and illustrate certain of their cases ; Professor J. Lorrain Smith, for his sympathetic interest and helpful and suggestive criticisms ; the Carnegie Trust for a grant to one of us ; and the very kind friend, who prefers to remain anonymous, whose generosity has defrayed the expenses of this research.

CORRECTION.

We regret that in the 'Description of Figures' (p. 189) in Part IV of the "Studies in Pneumonia in Childhood" certain numerical errors occurred. In the following the necessary corrections have been made.

DESCRIPTION OF FIGURES.

PART IV, PAGE 189.

Fig. 5 (×2.). (Case I. Male, aged 6 months.) Ulcerative bronchitis and confluent broncho-pneumonia in right upper lobe. Bronchi distinctly enlarged; majority filled with pus B = bronchus illustrated in Fig. 9.
Fig. 7 (×2½.). (Case IV. Female, aged 15 months.) Early bronchiectasis in right lung. One cavity of considerable size towards pleural surface. Several other bronchi enlarged. Confluent broncho-pneumonia in relation to affected bronchi. Obliteration of interlobar fissure. B = portion of bronchiectatic cavity illustrated in Fig. 11.
Fig. 8 (×2.). (Case V. Female, aged 16 months.) Early chronic bronchiectasis with terminal acute pneumonia in left lung. B = bronchus illustrated in Figs. 14 and 15.
Fig. 9 (×60.). (Same case as Fig. 5.) Ulcerative bronchitis. Bronchial wall completely destroyed and margin of cavity formed by consolidated alveoli. Plug of pus in lumen.
Fig. 10 (×60.). (Same case as Figs. 5 and 9.) Ulcerative bronchitis. Bronchial wall completely destroyed at one side (A) and relatively healthy at the other.
Fig. 11 (×110.). (Same case as Fig. 7.) Early bronchiectasis. Diverticulum of large cavity. Reconstitution of wall by granulation tissue.
Fig. 14 (×60.). (Same case as Fig. 8.). Bronchus in which disintegration and erosion of half of the circumference had occurred and in which repair was in process. Intact wall on the left; denuded and excavated wall on the right of the field. A = portion of wall shown in Fig. 15.
Fig. 16 (×120.). (Same case as Fig. 4.) Wall of damaged, slightly dilated, bronchus. Whole thickness of wall composed of very vascular fibrous tissue, infiltrated with inflammatory cells; muscle absent. Epithelial lining formed of several layers of small cuboidal cells.
Fig. 17 (×300.). (Same case as Fig. 6.) Obliterative bronchiolitis. Original wall of bronchus destroyed. Organisation of exudate in lumen by young fibroblasts in process and leading to obliteration. Small amount of pus still present in centre.
Fig. 18 (×300.). (Same case as Figs. 8, 14 and 15.) Organizing pneumonia. Alveolar space seen, partly occupied by a mass of proliferating fibroblasts and young connective tissue fibres attached to the wall at one point. A few inflammatory cells, remnants of exudate, present.
Fig. 19 (×120.). (Same case as Figs. 4 and 16.) Chronic fibrosis of lung, with obliteration of alveoli. A few remnants of alveolie represented by small epithelial lined spaces. Dense aggregation of lymphocytes marks site of obliterated bronchus.

In the Text.

Page 180, line 29, for Case I substitute Case III.
Page 183, sixth line from bottom, for Case IV substitute Cases III and V.
Page 184, line 10 from top, for Fig. 15 substitute Fig. 17.

NOTE ON THE BACTERIOLOGY OF BRONCHO-PNEUMONIA OF CHILDREN.

BY

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Invited by Drs. McNeil, Macgregor and Alexander to co-operate with them in the study of broncho-pneumonia in children and to investigate the bacteriological cause of this very fatal malady, I was summoned to attend the first post-mortem examination of their series on the 25th February, 1926. Two fatal cases of broncho-pneumonia (see Appendix, Cases 1 and 2) were examined on that day. The naked-eye post-mortem appearances in both cases reminded me of that type of fatal broncho-pneumonia which occurs in certain cases of influenza, and of which I had seen many examples during the terrible epidemic of 1917—18 in Bombay and India. The work then carried through in co-operation with my colleagues at the Bombay Bacteriological Laboratory, had shown that, while it was comparatively easy to demonstrate the presence of Pfeiffer's bacillus by culture when a special medium was used, it was much more difficult to do so when the ordinary laboratory media were employed, including in this category blood agar.

To the post-mortem examinations above mentioned I had brought with me for use a variety of the culture media generally employed in routine laboratory investigations, (for example, agar, serum agar, and blood agar), but I had not brought with me any special medium essential for the study of influenza, as I had not imagined that I might be called upon to study a complication of that disease. For these two first examinations, therefore, I had to make use of such media as were at hand, but in addition to cultures from the lungs and sputum, I prepared smears from the sputum and inflamed lung. These smears were examined after staining by Gram's method ; they revealed the presence of large numbers of minute Gram-negative bacilli having the morphological characters of Pfeiffer's organism. The organisms were more abundant in the sputum of both cases, but they were also demonstrated in the smears from the lungs. In the first of the two cases, although Pfeiffer's bacillus preponderated, other organisms were also present, but in the lung smears only Pfeiffer's bacillus could be seen. Pfeiffer's bacillus was also isolated from a culture made from the lung in Case No. 2.

Technique Employed.

In all subsequent examinations a special medium, Soparkar's, was used for cultivations. This medium has been found to be very suitable for the detection of Pfeiffer's bacillus. The method of preparing the medium has been described in the Indian Journal of Medical Research[1]. In addition to the fact that Pfeiffer's bacillus grows well on this medium it has this advantage over many of the other media used for the cultivation of that organism : it is transparent, so that it is possible to study the characters of the colonies which develop upon it by transmitted as well as reflected light. This is a matter of considerable moment in distinguishing colonies of Pfeiffer's bacillus from other colonies simulating it.

A routine system of examination was carried through in all cases where this was possible. After the chest had been opened and the pericardium incised, the surface of the heart was seared with a hot iron, and by means of a sterile capillary pipette and teat, passed through the sterilized surface of the heart, a sample of the blood in the heart was withdrawn and spread on the surface of a Soparkar agar slope. The lungs were then removed from the chest, a consolidated area was selected, the surface of the pleura over this area was seared and a capillary pipette with teat attached was passed through the seared pleura into the consolidated tissue immediately below the surface of the pleura, and by manipulating the teat and capillary tube a small quantity of blood-stained fluid was obtained. A small drop of this fluid was placed in the centre of a Petri dish filled with Soparkar's medium, and with a sterile glass rod, bent at a right angle, the drop of fluid was spread over the surface of the plate. Such cultures may be called for convenience lung-puncture cultures. In a similar manner a plate was prepared from the sputum which was usually withdrawn from the trachea by means of a capillary pipette. These may be designated sputum cultures. Slides for microscopical examination were prepared at the same time. In almost all the cases the lymphatic glands at the hilum of the lungs were much enlarged and inflamed, but it was only in three cases at the end of the series that cultures were made from this source. Where there was an excess of fluid or pus in the pleura, pericardium, or peritoneum, cultures were made from the fluid, and, when meningitis was present, material from this source was also examined bacteriologically. In a few instances, when I was unable to be present at the post-mortem examination, *e.g.*, Cases 10 and 16, the lungs and certain other organs were sent to me at the laboratory from the hospital. All the autopsies were made within 24 hours of death.

Adopting this method of examination forty cases of broncho-pneumonia were examined during a period extending from 25th February, 1926, to the 19th February, 1929. Some of the main features of this investigation are detailed in the Appendix.

Bacteriological Results.

In 33 out of the 40 cases a pure culture of Pfeiffer's bacillus was obtained from one source or another. In these cases it was possible to apply certain bacteriological tests for the identification of the strains isolated. The most important criterion for identifying Pfeiffer's bacillus is the fact that this organism grows on a special medium containing blood which has been modified by heat, and that it fails to grow on ordinary nutrient agar. Certain other tests were also applied such as ability to produce indol; ability to ferment glucose, galactose, xylose, fructose and in certain cases maltose with the production of acid but no gas. Certain agglutination reactions were also carried through. It is unnecessary here to enter into the details of these findings.

In five other cases, for one reason or another, a pure culture of Pfeiffer's bacillus was not obtained, though these organisms were recognized to be present by microscopical examination. In Case 1, for example, a suitable medium was not available for the cultivation of the organism; in Cases 4 and 19, owing to the abundant development of other organisms on the culture medium, it

was not possible to isolate the bacillus in pure culture, and in Cases 21 and 29 owing either to some defect in the cultivating medium, or possibly to some error in the technique of preparing the cultures from the lungs, both specimens were sterile. The culture from the sputum in Case 21 was also sterile. In Case 29, no plates being available, a series of agar slopes were employed and this in some measure explained the failure to isolate Pfeiffer's bacillus, although the organism was seen to be abundantly present in slides examined by the microscope. In these cases, if a microscopical examination can be relied on for identification, (admittedly a feeble method but of some value in experienced hands), Pfeiffer's bacillus was recognized. If these five cases are included with the 33 first mentioned then Pfeiffer's bacillus was demonstrated in 38 out of the 40 cases examined, *i.e.*, 95 per cent.

In two cases only out of the 40 (No. 20 and 23) no evidence was obtained that Pfeiffer's bacillus played any part in the cause of the condition. They were cases of extensive suppuration of the lungs and in this respect they resembled Case 38. In this latter case, however, a culture was made from an enlarged gland at the hilum of the lung and here Pfeiffer's bacillus was still to be found, although in all other situations it had been completely replaced by a vast number of all sorts of bacteria. Possibly, if a lymphatic gland had been similarly examined in Cases 20 and 23, Pfeiffer's bacillus might have been revealed.

Discussion.

The statement that Pfeiffer's bacillus was found in 95 per cent. of the cases examined is in itself of little value in deciding whether this organism is the cause of broncho-pneumonia in children; other facts must be taken into consideration. Among the most important of these is the fact that in early and acute cases (for example, Cases 3, 5, 9, 12, 14, 22, 26, 31, 34, 35, 36, 39) the lung-puncture culture gave an almost pure growth of Pfeiffer's bacillus. In the sputum culture of these cases colonies of Pfeiffer's bacillus were numerous, but colonies of other organisms were also present, the latter being particularly numerous in Cases 35 and 36. Where the final issue had been still further prolonged, or where secondary infection by a particularly virulent organism had occurred, *e.g.*, Cases 6, 8, 13, 18, 24, the lung-puncture culture showed the presence of other organisms in addition to Pfeiffer's bacillus, and in the same cases the sputum cultures showed that these other organisms were present in still larger numbers. In cases which had progressed to a further stage of development, Cases 10 and 15, for example, colonies of Pfeiffer's bacillus were now scarcely to be found in the sputum cultures, although more numerous in the lung-puncture cultures. In certain more advanced cases, No. 4, 20, 23, 38, where secondary invasion by all kinds of bacteria, but especially streptococci, had brought about the formation of multiple abscesses, Pfeiffer's bacillus could not be isolated from either the sputum or lung cultures. In Case 38 however, a few colonies of Pfeiffer's bacillus were obtained in a culture made from an enlarged lymphatic gland at the hilum of the lung. No culture from a similar source was made in the other cases of this group.

A careful and critical consideration of the evidence obtained during the examination of this series of 40 cases (some of this evidence has been detailed

above but other observations more difficult to describe and record have been omitted), leaves little doubt in my mind that Pfeiffer's bacillus is the primary agent in causing the type of broncho-pneumonia which we have studied. This organism appeared to upset the normal resistance of the tissues of the respiratory tract against invasion by bacteria, so that organisms, which are found in limited numbers and strictly confined to the mucous surfaces of the respiratory tract in healthy persons, multiply greatly, invade and destroy the tissues, causing the development of abscesses in the lungs, or extending into the serous sacs cause suppuration there, or invading the blood give rise to a septicæmia or more rarely pyæmia.

Before referring to these organisms of secondary importance a word or two may be said about Pfeiffer's bacillus itself. This organism generally exercises its harmful effects locally, but occasionally it may gain access to the blood directly or through the lymphatic channels. It was present in the heart blood in pure culture in one case only, No. 3, but it was present in this situation with other organisms in five other cases. In Cases 11 and 12 it was present in the circulating blood together with streptococci: in Case 9 with a coliform organism and staphylococci; in Case 25 with a coliform organism and pneumococci, and in Case 28 together with two distinct types of pneumococcus. It was also present in pure culture in the cerebro-spinal fluid in Case 9, and was recovered from this situation before death. It was isolated in pure culture from the recent adhesions in the pleural cavity of Case 3, and from the pus in the pleural cavity together with pneumococci in Case 12. It was probably present, though not isolated in pure culture, together with pneumococci and streptococci in the pus from the pleural cavity of Case 15. It was recovered from the pericardial fluid where it was present with pneumococci in Case 22. Without doubt this organism spreads along the lymphatic channels, for out of three examinations it was recovered twice from the enlarged glands at the hilum of the lungs, *i.e.*, in Cases 38 and 40.

Referring next to the secondary invading organisms, a streptococcus was most frequently found in the heart's blood. This organism was isolated in pure culture from this source in six cases, No. 4, 6, 7, 32, 33 and 36, and was present in two other cases, No. 11 and 12, together with Pfeiffer's bacillus. Streptococci were sometimes very abundantly present in the lungs, especially in cases where suppuration and abscess formation had developed, *e.g.*, Cases 4, 20, and 23. Streptococci were occasionally met with in the serous cavities; for example, in the peritoneum in pure culture in Case 30, and in the pleura, with other organisms, in Case 15.

Pneumococci were more rarely found in the blood. This organism was recovered in pure culture in this situation in Case 8, and was present with Pfeiffer's bacillus in two other cases, No. 25 and 28. In the latter case two distinct types of pneumococcus were present in the blood at the same time.

Some type of pneumococcus was most often found in cases which developed empyema, *e.g.*, No. 22, 28 and 30. It was also present in the meninges in Case 22.

The most striking instance of secondary infection was found in Case 30 where a streptococcus was present in pure culture in the peritoneum, and a

pneumococcus in the pleura, while Pfeiffer's bacillus was obtained in the lung-puncture culture almost uncontaminated with other organisms.

The question may be raised how far these cases of broncho-pneumonia are related to influenza. It is certain that the cases occurred in definite groups. As many as ten cases occurred in the months of February and March 1926; then a series of scattered cases, numbering in all eighteen, followed during the next eight months; another series of nine cases was examined in one month. It was definitely proved that the last group of cases occurred during a well marked epidemic of influenza in the city. Be this as it may, the bacteriological findings are just those met with in cases of influenzal broncho-pneumonia in adults, and if this fatal broncho-pneumonia of children is a manifestation of influenza, as I believe it is, then, coincidently with the appearance of cases of broncho-pneumonia, there should occur cases of capillary bronchitis, bronchitis, laryngitis and tonsillitis, diseases brought about by the same infection, but with decreasing degrees of extension of the virus along the respiratory tract in the order mentioned.

The question of the cause of influenza and its relation to Pfeiffer's bacillus has been well stated by Professor Muir[2] so long ago as 1919 when he wrote* :

"The question comes to be whether B. influenzæ (i.e. Pfeiffer's bacillus) is the essential cause of the disease or whether it is merely associated with an undiscovered virus, possibly ultra microscopic as some have supposed. Microscopical examination of sections show that the influenza bacillus is specially related to the broncho-pneumonia, a special feature of influenza, it is often the predominant organism and may abound not only in the bronchioles but in the air vesicles beyond. In other words a lesion, common in influenza, and rare apart from it, is associated with the appearance of this delicate organism in large numbers and this lesion represents the farthest extension of bacterial growth in a downward direction; it seems not unlikely that B. influenzæ is the agent which so markedly lowers the general resistance of the bronchial passages. Thus it may be the real cause of the disease. On the other hand there is the possibility that the presence of an ultra-microscopic organism underlies all the phenomena and the results of further investigation on this point must be awaited. But in any case it appears to us that Pfeiffer's bacillus plays a very important part in the production of the characteristic lesions."

This is neither the time nor the place to enter into a discussion on this subject which must be deferred to a more suitable occasion.

Conclusions.

Two general conclusions may be drawn from this investigation, First, that Pfeiffer's bacillus (*B. influenzæ*) is intimately associated with the broncho-pneumonia of children; and secondly, that this organism opens a path to the invasion of the body by secondary organisms, particularly streptococci, pneumococci, and staphylococci, as well as other organisms. The latter organisms may be found in the blood, causing septicæmia or pyæmia, in the serous cavities giving rise to empyema, peritonitis, or pericarditis; and they are frequently the cause of abscess formation in the lungs.

REFERENCES.

1. Liston, W.G., *Indian J. Med. Res.*, Calcutta, VI, 418.
2. Muir & Wilson, *Brit. Med. J.*, Lond., 1919, i, 3.

APPENDIX.

Notes on Cases Investigated.

Case. 1. K. G., aged 2 years, 4 months, died 25.2.26, after illness of 4 days. P.M. diagnosis, broncho-pneumonia with some confluence; Pfeiffer's bacillus microscopically in the sputum. No special media available for culture.

Case 2. A. A., aged 7 months, died 25.2.26, after illness of 8 days. P.M. diagnosis, confluent broncho-pneumonia; Pfeiffer's bacillus on blood agar from the lung and microscopically abundantly present in sputum and lung films.

Case 3. J. F., aged 1 year, died 6.3.26, after illness of 12 days. P.M. diagnosis, broncho-pneumonia with early confluence; a pure growth of Pfeiffer's bacillus from the heart, that organism also recovered from the lung and recent pleural adhesions.

Case 4. D. F., aged 1 month, died 8.3.26, after 1 day of apparent illness. P.M. diagnosis broncho-pneumonia of fulminating hæmorrhagic type; streptococcus from the heart, in pure culture. Numerous streptococci from lung abscess. Microscopically sputum showed numerous streptococci and a few gram negative bacilli, like Pfeiffer's bacillus.

Case 5. T. K., aged 1 year, died 8.3.26, after illness of 7 days. P.M. diagnosis, broncho-pneumonia confluent in the lower lobes; Pfeiffer's bacillus in pure culture from lung; heart blood sterile.

Case 6. M. D., aged 1 year, 4 months, died 12.3.26, after 26 days illness. P.M. diagnosis, broncho-pneumonia with bronchiectasis; streptococcus pure culture from heart, lung culture showed streptococci, Pfeiffer's bacillus, and diphtheria, the latter was proved to be virulent.

Case 7. R. M., aged 2 years, 4 months, died 15.3.26, after 35 days illness. P.M. diagnosis, broncho-pneumonia with abscess formation; Pfeiffer's bacillus from abscess, streptococci from heart, sputum contained diphtheria proved to be virulent.

Case 8. H. M., aged 1 year, 1 month, died 18.3.26, after 17 days illness. P.M. diagnosis, confluent broncho-pneumonia with early bronchiectasis; a pure culture of pneumococcus from the heart, Pfeiffer's bacillus, pneumococcus, and micrococcus catarrhalis from the lung and sputum.

Case 9. T. P., aged 9 months, died 26.3.26, after 12 days illness. P.M. diagnosis, broncho-pneumonia with meningitis. Pfeiffer's bacillus was recovered in a pure culture from the cerebro-spinal fluid during life; a mixed culture of Pfeiffer's bacillus, staphylococci and a coliform organism from the heart; lung culture almost pure Pfeiffer's bacillus.

Case 10. M. L., aged 6 years, died 31.3.26, after 8 days illness. P.M. diagnosis, old bronchiectasis with recent broncho-pneumonia; lungs sent to the laboratory where pus from abscess was found to contain many streptococci, a few Pfeiffer's bacilli, lung cultures showed some Pfeiffer's bacilli, many streptococci, staphylococci, pneumococci and other otganisms.

Case 11. C. B., aged 5 years, died 5.11.26, after 13 days illness. P.M. diagnosis, empyema with well defined abscesses at base of lungs; a mixed culture of Pfeiffer's bacillus with streptococci from the heart; lung cultures showed many streptococci, some Gram-negative bacilli, and M. catarrhalis.

Case 12. G. M., aged 2 years, 6 months, died 10.11.26, after 12 days illness. P.M. diagnosis, mixed broncho- and lobar pneumonia; pleural fluid contained many pneumococci but some Pfeiffer's bacilli; lung culture, practically pure Pfeiffer's bacilli; sputum, a mixed culture of Pfeiffer's bacilli and streptococci.

Case 13. M. D., aged 10 months, died 18.11.26, after 22 days illness. P.M. diagnosis, lobar pneumonia; Pfeiffer's bacillus, pneumococci and catarrhalis from lung culture; heart culture sterile.

Case 14. A. C., aged 2 months, died 1.12.26, after 10 days illness. P.M. diagnosis, broncho-pneumonia with extensive collapse. Pfeiffer's bacillus from throat before death, pure culture of Pfeiffer's bacillus from lung, heart sterile.

Case 15. J. S., aged 1 year and 3 months, died 1.12.26, after 75 days illness from long continued broncho-pneumonia with bronchiectasis and empyema, pus from pleura showed Gram negative bacilli with pneumococci and streptococci, a few colonies of Pfeiffer's bacillus from the sputum. Heart blood sterile.

Case 16. J. K., aged 1 year, 1 month, died 13.12.26, after 14 days illness from broncho-pneumonia with moderate confluence and some dilatation of the bronchi; organs sent to the laboratory, where from the lung culture six colonies of Pfeiffer's bacillus were recovered; pneumococci and streptococci were isolated from the spleen.

Case 17. R. A., aged 3 years, 7 months, died 14.12.26, after 7 days illness, This was a case of broncho-pneumonia following measles; a rich culture of Pfeiffer's bacillus was obtained from the sputum. Heart culture sterile.

Case 18. G. M., aged 4 years, died 18.2.27, after 15 days illness from broncho-pneumonia with irregular confluence; Pfeiffer's bacillus and streptococci from the lung, these organisms together with diphtheria were isolated from the suptum; heart culture sterile.

Case 19. T. C., aged 1 year and 5 months, died 28.2.27, after 45 days illness, from pulmonary tuberculosis with super-added acute pneumonia; sputum showed abundant colonies of a Gram negative bacillus with numerous colonies of pneumococci and streptococci. Pfeiffer's bacillus, however, was not isolated in pure culture; heart blood culture sterile.

Case 20. J. M., aged 1 year and 4 months, died 3.5.27, after an illness of 25 days. This was a typical lobar pneumonia with suppuration; streptococci, catarrhalis and pneumococci together with a Gram negative bacillus (which was not Pfeiffer's bacillus) were isolated from the cultures in this case; no evidence of the presence of Pfeiffer's bacillus was obtained; heart blood culture was sterile.

Case 21. M. R., aged 8 months, died 21.3.27, after 37 days illness from confluent broncho-pneumonia with empyema; numerous bacilli morphologically resembling Pfeiffer's bacillus were present in the sputum, the cultures however were sterile; heart blood culture sterile.

Case 22. G. T., aged 1 year, died 22.3.27, after 16 days illness from broncho-pneumonia with pericarditis, empyema, and cerebro-spinal meningitis; cultures from the sputum gave an abundant growth of Pfeiffer's bacillus; cultures from the lungs and cerebro-spinal fluid were sterile; the pericardial fluid gave a mixed culture of Pfeiffer's bacillus with pneumococcus; heart culture was sterile.

Case 23. B. H., aged 5 months, died 24.3.27, after 10 days illness from confluent bronch-pneumonia; the bacterial feature of the sputum viewed microscopically was the large number of streptococci present; cultures from the sputum gave streptococci, staphylococci, together with a diphtheria-like bacillus. Similar organisms in the lung culture, no Pfeiffer's bacilli seen; heart culture sterile.

Case 24. J. C., aged 9 months, died 24.3.27, after 5 days illness from confluent broncho-pneumonia; sputum showed many colonies of Pfeiffer's bacillus with some staphylococci and pneumococci; heart culture sterile.

Case 25. M. L., aged 1 year, died 27.3.27, after 35 days illness from confluent broncho-pneumonia with empyema; the lung culture in this case gave an almost pure growth of Pfeiffer's bacillus; a mixed culture of Pfeiffer's bacillus, a type of pneumococcus, and a coliform bacillus was obtained from the heart.

Case 26. A. D., aged 2 years 3 months, died on 5.4.27, after 10 days illness from discrete broncho-pneumonia; a practically pure culture of Pfeiffer's bacillus was obtained from the lung; the sputum showed many colonies of Pfeiffer's bacillus but the heart blood was sterile.

Case 27. R. P., aged 1 year, 5 months, died 7.5.27, after 8 days illness from broncho-pneumonia with some confluence; the lung culture showed many colonies of Pfeiffer's bacillus with catarrhalis and staphylocci; the sputum culture also showed many colonies of Pfeiffer's bacillus.

Case 28. G. S., aged 7 months, died 6.6.27, after 21 days illness from a typical lobar pneumonia with empyema; the pleural fluid gave a pure growth of pneumococcus; the sputum culture showed many colonies of Pfeiffer's bacillus; the lung culture also showed many colonies of Pfeiffer's bacillus but some colonies of pneumococcus and catarrhalis were also present; the heart culture was a mixed growth of Pfeiffer's bacillus with two distinct types of pneumococci.

Case 29. W. T., aged 5 months, died 31.10.27, after 3 days illness from broncho-pneumonia with acute peritonitis; the culture from the heart was sterile, so also was the culture from the lung; the peritoneal exudate showed many streptococci; in the sputum many minute Gram negative bacilli like Pfeiffer's bacillus were seen microscopically but no culture of that organism was recovered.

Case 30. A. A., aged 1 year, 3 months, died 24.1.28, after 40 days illness from broncho-pneumonia and empyema; the peritoneal exudate gave a pure culture of streptococci; the pleural fluid contained typical pneumococci while the culture from the lung gave an almost pure growth of Pfeiffer's bacillus.

Case 31. D. L., aged 1 year, 6 months, died 14.11.28, after 8 days illness from confluent broncho-pneumonia; almost a pure culture of Pfeiffer's bacillus was obtained from the lung and these organisms were abundant in the culture from the sputum; the heart culture was sterile.

Case 32. I. P., aged 5 months, died 5.2.29, after 21 days illness from partially confluent broncho-pneumonia; sputum culture showed many streptococci and some colonies of Pfeiffer's bacillus; the lung culture gave an almost pure growth of Pfeiffer's bacillus; the heart culture gave a pure growth of a streptococcus.

Case 33. L. M., aged 9 months, died 5.2.29, after two days illness. This child died after a fit. A small patch of pneumonia was found in one lung; the sputum culture showed many streptococci and catarrhalis but some Pfeiffer's bacillus colonies were also obtained; the lung culture was almost pure Pfeiffer's bacillus, the heart culture gave a pure streptococcus.

Case 34. R. B., aged 2 years, died 7.2.29, after 30 days illness from discrete broncho-pneumonia with empyema; the lung culture gave pure Pfeiffer's bacillus; the pus from the pleura gave a pure growth of a type of pneumococcus; the heart culture was sterile.

Case 35. R. R., aged 3 years, died 8.2.29, after 14 days illness from broncho-pneumonia; the lung culture showed a pure growth of Pfeiffer's bacillus; the sputum culture contained many colonies of that bacillus with other organisms, the heart culture was sterile.

Case 36. A. G., 1 year, 2 months, died 11.2.29, after 10 days illness from discrete broncho-pneumonia; the long culture was almost pure Pfeiffer's bacillus and the sputum culture showed a few colonies of that bacillus with many streptococci and other organisms, the heart culture was sterile.

Case 37. J. A., aged 2 years 4 months, died 11.2.29, after 7 days illness from tubercular meningitis with broncho-pneumonia; colonies of Pfeiffer's bacillus were abundant in the sputum culture. No other cultures were made as the organs had been removed before I arrived at the autopsy.

Case 38. J. S., aged 5 years, died 12.2.29, after 18 days illness from broncho-pneumonia with multiple abscess formation; the abscesses were so numerous that a lung puncture could not be made without entering a small abscess cavity; the sputum swarmed with organisms. No Pfeiffer's bacilli were recovered from the usual sources but in this case a culture was made from a gland at the hilum of the lung, from this a few colonies of Pfeiffer's bacillus were obtained with colonies of other organisms.

Case 39. S. M., aged 2 years, 11 months, died 19.2.29, after 14 days illness from broncho-pneumonia; an almost pure culture of Pfeiffer's bacillus was obtained from the lung; the sputum culture showed an abundant growth of that organism. A culture from a lymph gland at the hilum of the lung and from the heart were sterile.

Case 40. J. R., aged 8 months, died 19.2.29, after 11 days illness from broncho-pneumonia which was confluent in one lung and early in the other; numerous colonies of Pfeiffer's bacillus were obtained in the lung culture mixed with other organisms; a few colonies of Pfeiffer's bacillus were also found with some other organisms in a culture made from a lymph gland in the lung.

THE ACID-BASE EQUILIBRIUM OF THE BLOOD IN ACUTE RHEUMATISM.

BY

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One of the earliest conceptions of the nature of acute rheumatism was based upon the humoral theory and assumed that the pain of the disease was due to the flow of rheum from the brain and its final localization in the affected parts. Later this explanation was displaced by a chemical one. Thus some fifty to sixty years ago Maclagan[1] wrote as follows :—

> One of the characteristics of acute rheumatism is the occurrence of profuse acid perspiration. The urine is hyperacid, and even the naturally alkaline saliva may have an acid reaction. This excessive acidity naturally led to the hypothesis that an acid condition of the blood had something to do with the production of the rheumatic symptoms. Dr. Prout made the definite suggestion that the materies morbi was lactic acid, and that the rheumatic symptoms resulted from the accumulation of this acid in blood.

The acid theory, which possessed the advantage of a rational explanation of the then usual treatment by alkalies, was very generally held for a time ; but now that the infective origin of acute rheumatism is commonly accepted, the question whether the causal organism may be one that produces an acid toxin has been raised. It therefore occurred to us that an investigation of the acid-base balance of the blood in rheumatism should give some evidence for or against this suggestion.

Theoretical Considerations.

It is well known that although normally the pH of the blood is extremely constant, certain pathological conditions and some experimentally produced abnormal states, can alter its value either in the direction of an acidosis or an alkalosis. Usually, however, any change tending to occur is speedily regulated by alterations in the excretory systems, which neutralize the disturbing effect and keep the pH constant. This is not always so, and as soon as the regulating mechanism breaks down, or its capacity becomes exhausted, a permanent alteration of pH is produced.

Alkali is contained in the blood mainly in the form of bicarbonate bound to sodium and other bases. The ratio or this to the free carbon dioxide determines the acidity, or pH, ot the blood, and is represented as $\frac{BHCO_3}{H_2CO_3}$ where the $BHCO_3$ is the total base bound to bicarbonate, and H_2CO_3 the free CO_2. It will be seen that either an increase in $BHCO_3$ or a decrease in H_2CO_3 will tend to have the same effect, a shift in the alkaline direction, or an ' alkalosis,' with a consequent increase of pH ; similarly a decreased $BHCO_3$ or an increased H_2CO_3 will tend to produce an acidosis, indicated by a lower pH.

That this change in pH is not generally obtained is due to the compensation described above. For example, an alkalosis due to decreased H_2CO_3 through increased breathing and consequent rapid removal of CO_2 from the blood, will be compensated by increased excretion of the base in the urine which will become alkaline in reaction. This tends to restore the ratio $\frac{BHCO_3}{H_2CO_3}$ to normal. The condition is found in individuals breathing air at high altitudes, where the oxygen tension is low. An acidosis may be produced by increased formation of non-volatile acids in the body, as in diabetes ; or by their faulty excretion, as in nephritis. Violent muscular exertion, with formation of lactic acid, has a similar result. Compensation will be effected by increased respiration which, by rapid elimination of carbon dioxide, lowers the acidity towards normal, but should a point be reached where the regulating mechanism is unable to cope with the disturbing factor, as for example in a case of diabetes where the production of non-volatile acids is continuous, the pH will be altered, and an abnormal figure obtained. This is the condition of uncompensated acidosis.

For a knowledge of the acid-base balance or equilibrium of a given specimen of blood two estimations are necessary, the pH and the carbon dioxide content. The latter figure is not to be confused with the term ' alkali reserve.' Carbon dioxide is present in the blood in two states, partly free, dissolved physically in the plasma, and partly combined with alkali in the form of bicarbonate. It is the combined CO_2 which is referred to by the term ' alkali reserve,' while the figure obtained in estimating the acid-base equilibrium is that of the total CO_2. The reason that so little distinction is made between the two values is that the free CO_2, besides being only a small fraction (5%) of the total is an extremely constant quantity. Hence variations in the total CO_2 may be ascribed exclusively to the bicarbonate portion, or alkali reserve.

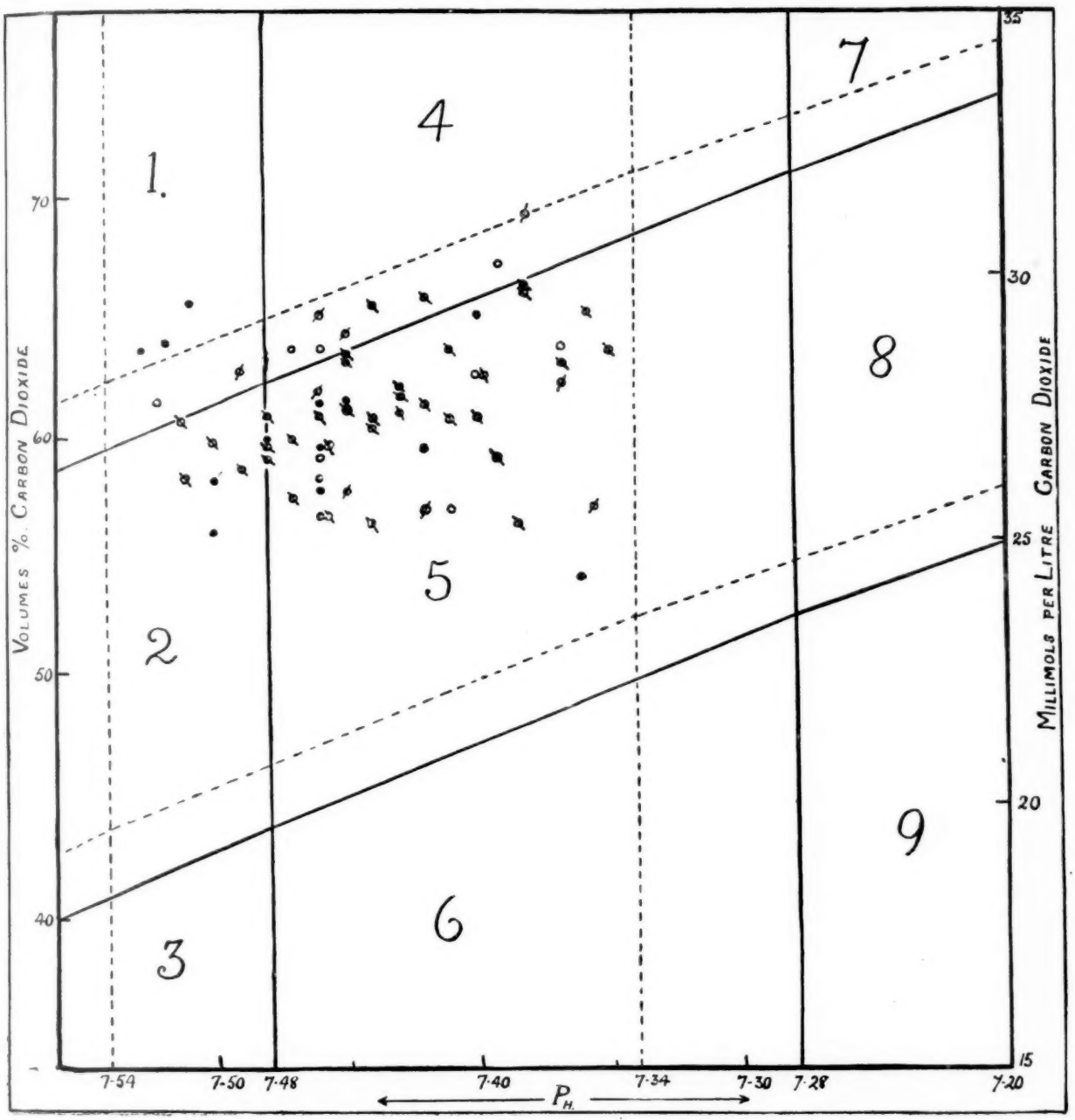
Present Investigations.

In this work the pH was determined electrometrically, using a quinhydrone electrode of the micro-form devised by Cullen and Billmann[2], and the carbon dioxide by Van Slyke's method. For illustrating the results obtained use has been made of Van Slyke's graph (see Fig. 1). The ordinates give the CO_2, the abscissæ the pH. The heavy lines show the extreme limits for normal blood which Van Slyke has adopted from figures given by different workers. We have ourselves obtained a higher pH range than that given, probably due to the use of the quinhydrone electrode, which was not in use when Van Slyke's figures were obtained. It will also be seen that a narrower range of results has been found for the CO_2 content. Our own ' normal limits ' are given in broken lines on the same chart.

The nine areas which are formed represent the nine possible conditions of the blood. The three in the centre column are those most commonly met, being the three with normal pH : that is, compensated CO_2 (or alkali) excess and deficit respectively, and the normal area.

From the acid-base figures alone it is, of course, impossible to say whether a high CO_2 result is a compensated alkali or CO_2 excess ; that is, whether excess

FIG. I.



● Normal.
○ Children's Hospital.
Ø Moseley Hall Convalescent Hospital.
Ø Baskerville School.

of alkali was the primary disturbance compensated by CO_2 retention, or excess of CO_2 compensated by alkali retention; the same is true for a compensated deficit. In either case clinical or further biochemical evidence may indicate the actual condition.

The total CO_2 is given at the two sides of the chart as volumes per cent carbon dioxide and millimols per litre. The latter, which is obtained by dividing volumes per cent by 2·226, is the nomenclature more common among American workers.

The areas on the graph are as follows :—

1. Uncompensated alkali excess.
2 and 3. Uncompensated CO_2 deficit.
4. Compensated alkali or CO_2 excess.
5. Normal balance.
6. Compensated alkali or CO_2 deficit.
7 and 8. Uncompensated CO_2 excess.
9. Uncompensated alkali deficit.

Results of Investigations.

The treatment of children suffering from acute rheumatism in the City of Birmingham has been so organised that the patient may obtain continuous institutional treatment for a period of one to two years or even longer. The scheme has been outlined by Thomson[3] and briefly it aims at ensuring that the child shall have three different forms of treatment in three institutions :— (1) Treatment during the acute phase in the Children's Hospital; followed by (2) six to nine months in Moseley Hall Convalescent Hospital for Children, during the greater part of which time the child is kept in bed; after which (3) the child is transferred to Baskerville School, a residential school under the Education Authority. The average duration of time spent at this institution is about nine months.

For the purpose of this investigation the acid-base balance of the blood has been estimated in fifty-three cases drawn from all of the groups described above. By this means it has been possible to compare the results obtained from children in all stages of the disease, acute, convalescent and quiescent. For comparison with these the acid-base balance of the blood has been estimated in fifteen healthy elementary school children.

The results show that the normal and the rheumatic cases occupy the same area of the graph, there being no tendency for the pathological examples to group themselves in, or even to approach towards, any of the areas representing an abnormal condition.

Table 1 shows a summary of the results obtained.

TABLE I.

Summary of results in rheumatic and normal children.

	No. of Cases	pH.	CO_2 (vols. %)
Hospital	7	7·47	62·08
Moseley Convalescent Hospital	10	7·42	62·03
Baskerville School	36	7·43	60·87
Normal	15	7·46	59·34

Table 2 shows the details of the included cases.

TABLE 2.

DETAILS OF RESULTS IN RHEUMATIC AND NORMAL CHILDREN.

Series	Case No.	pH.	CO_2 Vols. %
Children's Hospital	1. D.H.	7·40	60·98
	2. A.W.	7·47	63·70
	3. L.M.	7·52	61·24
	4. K.H.	7·46	59·28
	5. H.M.	7·58	58·57
	6. D.S.	7·46	63·81
	7. L.P.	7·39	66·98
	Mean :	7·47	62·08
Moseley Convalescent Hospital	1. C.A.	7·46	65·17
	2. J.E.	7·45	64·42
	3. H.S.	7·38	71·11
	4. V.G.	7·49	62·76
	5. N.G.	7·46	59·69
	6. W.M.	7·35	57·52
	7. W.S.	7·42	57·05
	8. D.B.	7·45	57·74
	9. J.M.	7·36	62·30
	9. J.M.	7·36	62·30
	10. J.P.	7·40	62·47
	Mean :	7·42	62·03
Baskerville School	1. G.F.	7·42	56·84
	2. M.N.	7·38	66·10
	3. A.W.	7·36	47·40
	4. J.K.	7·40	60·88
	5. J.G.	7·45	61·34
	6. E.B.	7·44	60·70
	7. K.M.	7·51	58·17
	8. R.P.	7·51	60·50
	9. T.T.	7·38	66·51
	10. E.P.	7·35	62·28
	11. H.W.	7·40	62·45
	12. S.T.	7·50	59·90
	13. B.T.	7·38	56·17
	14. H.T.	7·36	62·93
	15. E.S.	7·44	56·10
	16. L.G.	7·46	60·83
	17. F.G.	7·44	65·37
	18. D.F.	7·44	62·17
	19. C.P.	7·46	63·16
	20. H.C.	7·37	68·12

TABLE 2.—*continued*

DETAILS OF RESULTS IN RHEUMATIC AND NORMAL CHILDREN.

Series.	Case No.	pH.	CO_2 Vols. %
Baskerville School (*contd.*)	21. L.M.	7·46	56·31
	22. T.P.	7·48	60·07
	23. C.H.	7·48	59·30
	24. O.P.	7·49	58·25
	25. H.L.	7·43	61·17
	26. K.C.	7·47	59·92
	27. D.W.	7·47	57·40
	28. F.V.	7·42	61·52
	29. D.S.	7·42	65·80
	30. E.J.	7·43	61·18
	31. R.B.	7·41	68·83
	32. A.P.	7·48	60·83
	33. S.R.	7·36	64·60
	34. D.B.	7·45	57·30
	35. M.G.	7·41	60·64
	36. R.V.	7·44	60·25
	Mean :	7·43	60·87
Normal	1. G.C.	7·50	58·06
	2. N.H.	7·52	64·07
	3. H.O.	7·46	61·35
	4. B.W.	7·46	58·15
	5. W.J.	7·40	65·10
	6. G.W.	7·48	59·91
	7. R.	7·46	57·85
	8. V.G.	7·45	61·58
	9. A.F.	7·46	56·70
	10. D.F.	7·46	59·70
	11. P.E.	7·51	65·50
	12. S.G.	7·50	55·85
	13. R.T.	7·42	59·55
	14. J.W.	7·36	54·21
	15. J.M.	7·44	53·54
	Mean :	7·46	59·34

DISCUSSION.

The only definite statement in the literature bearing on the acid-base equilibrium in acute rheumatism that we can trace is by Benzançon and Weill[4], who in a communication published last year state that the blood pH and the alkali reserve are normal in rheumatic patients. This paper does not contain details given of the number of cases examined, the state of the disease at the time of the examination, nor the methods used. Nevertheless we find ourselves in complete agreement with their statement.

Since our enquiry was started a book has been published on "Recent Advances in Pædiatrics" in which the authors (Pearson and Wyllie[5]) return to the idea of a chemical basis of the disease. They consider that the picture of a child with subacute attacks of rheumatism is similar to that of the fatigued man in whom the symptoms are due to excess of lactic acid in the muscles and other tissues and that "clinical evidence is overwhelming in support of the "'acid' basis of the disease." They regard the pains of rheumatism as caused primarily by excess of acid in the body, infection only accounting for 'some of the later effects.' Further, they say that there is a constitutional predisposition to acute rheumatism, and that the type of child which is likely to develop the disease can be recognized, and to this type they have given the title of the acid or hypercalcic child. In such children calcium and phosphorus are present in the tissues in excess, and whereas normally phosphorus is combined with calcium 'it is possible that in rheumatism phosphorus is present in excess of 'calcium.' Finally, we are invited to believe that chorea is due to an excess of phosphate which collects in the area of the brain where the circulation is most likely to stagnate, *i.e.*, in the cerebellum.

These authors have attempted to forestall possible criticism by saying,

> It is now recognized that it is an obvious fallacy to regard the blood as a criterion of the state of the tissues. The blood is merely a supply and drainage system which carries materials to be utilised or eliminated. It cannot be held to represent the actual conditions of the tissues which it serves. The blood is apparently normal, yet the tissues are acid.

Whilst it could be argued from first principles that the investigation of variations in the contents of a supply and drainage system might throw light on the changes which are taking place within the structures it serves, we prefer to answer this contention by the following quotation from a recent paper by Marriott and Hartmann[5].

> The actual composition of the tissue cells cannot be determined during life but it has been demonstrated, chiefly by the work of Van Slyke, that one can predict changes in the red blood cells from changes in the plasma by application of the Donnan principle of ionic and osmotic equilibrium existing when a membrance is not permeable to all the solutes present. It seems almost certain that a similar equilibrium exists between the lymph and the tissue cells, and it has already been shown that this equilibrium exists between the plasma and the lymph. Therefore by a study of the blood plasma is obtained a picture of the changes which are occurring at the same time within the cells.

We admit the correctness of Pearson and Wyllie's statement that a marked or prolonged change in reaction does not occur except as a fatal event, but would point out that there is such a thing as 'compensated acidosis,' and that in fact this actually occurs in the very condition of the excessive exercise or fatigue which they have invoked as comparable with the symptoms of subacute rheumatism. With regard to calcium they argue that an estimation of blood calcium is not an index of the calcium ions either in the circulatory or body fluids. Whilst it is true that the estimation of blood calcium does not give a direct indication of the calcium ions present, yet such an estimation is extremely useful for comparative purposes, since providing the pH of the blood remains constant, the blood calcium does give an indirect indication of ionic calcium.

In this paper we have only dealt with the acid-base equilibrium, but one of us (S.H.E.) has investigated among other factors variations in blood calcium in rheumatism, and the results obtained will shortly be published. The results obtained show that there is no experimental evidence in favour of the view that there is an excess of acid in the tissues of the rheumatic child. We have felt the importance of examining the point of view of these writers in some detail because already their statements are being accepted by examination candidates, many of whom have adopted both the hyper- and hypo-calcic child with a considerable, but in our view unmerited and misplaced, affection.

Conclusions.

1. The acid-base equilibrium of children suffering from acute rheumatism, whether in the acute, convalescent or quiescent stages of the disease, is normal.

2. There is no evidence in favour of the view that the symptoms of rheumatism are due to an excess of acid in the tissues, or that the rheumatic child is an ' acid ' child.

The expenses of these investigations were defrayed by the Medical Research Council to whom we would tender our thanks.

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THE CARBON DIOXIDE DISSOCIATION CURVE OF THE BLOOD IN INFANCY AND CHILDHOOD.

BY

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Since 1914 much work has been done on the CO_2 dissociation curve in health and disease. So far, with the exception of a few results published in 1923 by Conway-Verney[1] all the observations reported have been made on the blood of adults. The work described in this paper deals with the CO_2 dissociation curves of the blood of a group of normal children as well as a few with disturbances of acid-base equilibrium.

Methods of Investigation.

The method employed was essentially the same as that originally described by Christiansen, Douglas and Haldane[2]. For the analysis of the gas-mixtures, Haldane's air-gas analysis apparatus was used, while the Haldane blood-gas apparatus was employed for the blood. The water-bath accessories were slightly modified. Instead of an electric thermostat, a mercury one was used which controlled the temperature to within 0·5°C. quite satisfactorily. The apparatus was designed to hold two saturating flasks at once, so arranged as to revolve about a central axis, in this way obviating the necessity for a fan to keep the temperature constant throughout the bath. An approximately known amount of CO_2 was introduced into the saturating flask by means of a graduated burette to the lower end of which was attached a mercury reservoir. The upper end of the burette was fitted with a two-way stop-cock and two arms, one connecting with the reservoir of CO_2 and the other for attaching by means of rubber tubing to the saturating flask. After the gases in the flask had become mixed, the pressure in the flask was equalized with atmospheric pressure by a momentary release of the clip on the attached rubber tube.

In all our experiments fully oxygenated venous blood was used. Potassium oxalate and sodium fluoride in minute amounts were used in the syringe, the former to prevent clotting and the latter to prevent possible conversion of glucose into lactic acid, which by combining with base lowers the carbon-dioxide combining capacity of the blood (Lovatt-Evans[3]). It has been shown by several investigators that neither of these substances affects the CO_2 dissociation curve. The determinations were carried out in all cases within two hours of the withdrawal of the blood.

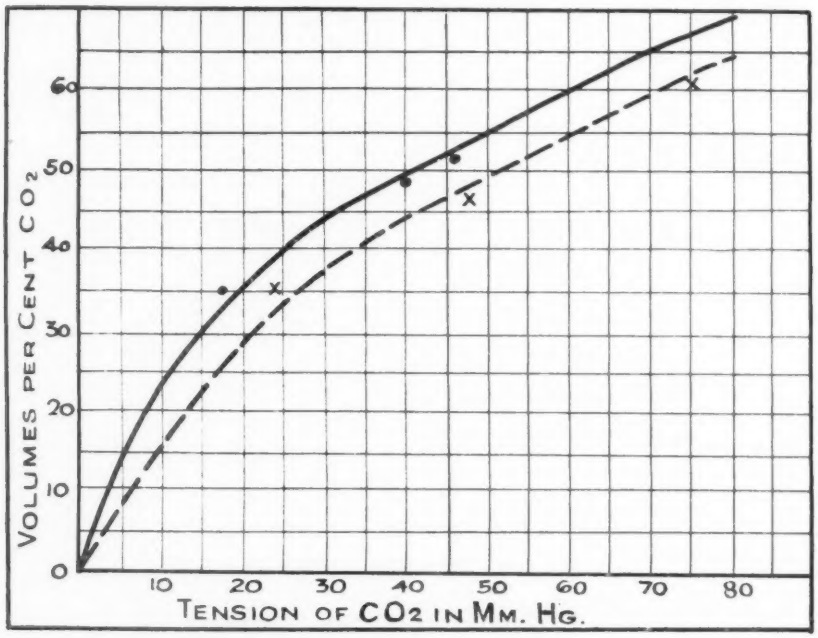
At least three determinations were made on each sample of blood. In every case the first tension of CO_2 to which the blood was exposed was between 35 and 40 mm. Hg. The gas mixture in the flask was then enriched with CO_2 so as to produce a tension of over 60 mm. Hg. Lastly the blood was exposed to a low tension at least below 25 mm. of CO_2. Haggard and Henderson[4] found that exposure of blood to low pressures of CO_2 led to an irreversible alteration of the H_2CO_3 : $NaHCO_3$ equilibrium. Lovatt-Evans[3] showed that this change was not necessarily due to low tensions of CO_2 but merely that it took place more rapidly under these conditions. It has been shown that blood exposed to a low partial pressure of CO_2 undergoes partial hæmolysis. The hæmoglobin thus liberated into the plasma probably acts as a weak acid and hinders the fixation of CO_2 by the base, with the result that the amount of CO_2 taken up at the various tensions of CO_2 is distinctly less in a hæmolysed than in a non-hæmolysed sample. Figure 1 illustrates an experiment which demonstrates the effect of hæmolysis. It will be seen that at a tension of 40 mm. Hg. laked blood takes up about 10 per cent. less CO_2 than does unlaked blood.

As laking is likely to occur at any tension less than 25 mm. Hg., and since the complete sample of blood is put into the saturating flask at the beginning of the experiment, it is desirable that the exposure to low tensions of CO_2 should be performed last. Otherwise hæmolysis may occur and vitiate the results.

The Normal Carbon Dioxide Dissociation Curve.

In Fig. 2 are plotted the points obtained at various tensions of CO_2 from the bloods of ten normal children whose ages varied from three months to ten years. The abscissa represents the CO_2 tension in mm. Hg. at 37·5° C. to which the blood was exposed. The ordinate represents the total amount of CO_2 (free and combined) taken up at any particular tension of CO_2. Twenty-three points

Fig. I



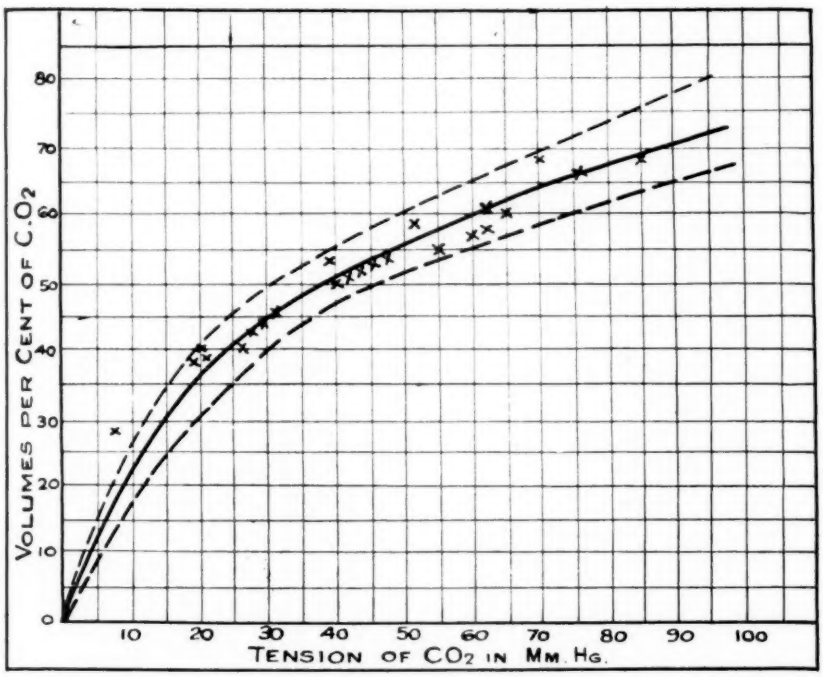
Continuous line and dots = Unlaked blood.
Broken line and crosses = Laked blood.

are marked and with the exception of one point at the low tension of 8 mm. (probably an error) all are within the limits indicated by the dotted lines. At a CO_2 tension of 40 mm. Hg., the total CO_2 content varied from 47 to 56 volumes per cent. with an average of 51·5 volumes per cent. which falls almost exactly on the curve for normal blood as determined by Christiansen, Douglas and Haldane[2]. It is convenient in describing CO_2 dissociation curves to indicate the position of each with reference to that of a standard at a tension of CO_2 equivalent to 40 mm. Hg. The standard generally used is the curve given by Haldane's blood which contains 51 volumes per cent. at 40 mm. Hg. tension of CO_2. If a curve shows 56 volumes per cent at this tension, this will be indicated by saying that it is 9·8 per cent. $\frac{56-51}{51} \times 100$ above the standard. The limits for our series of normals would thus be −8·9 to +9·8. In other words,

if the blood absorbs more CO_2 than normal, the curve is shifted to the left and may be spoken of as hypercapnic. If the blood absorbs less CO_2 than normal, it is shifted to the right and is therefore hypocapnic.

Peters, Barr and Rule[5] analysed the CO_2 dissociation curves in a series of normal adults, in all 18, 3 of their own and 15 collected from the literature. At a tension of 40 mm. Hg., they define the limits of normal as being from 43 to 56 vol. per cent. with an average of 49 vol. per cent., or in terms of Haldane's curve, −15·6 per cent to +9·8 per cent. In children in whom there is generally found evidence of a more unstable acid-base equilibrium, one might have expected that the limits of normal would at least have been wider than in

FIG. II



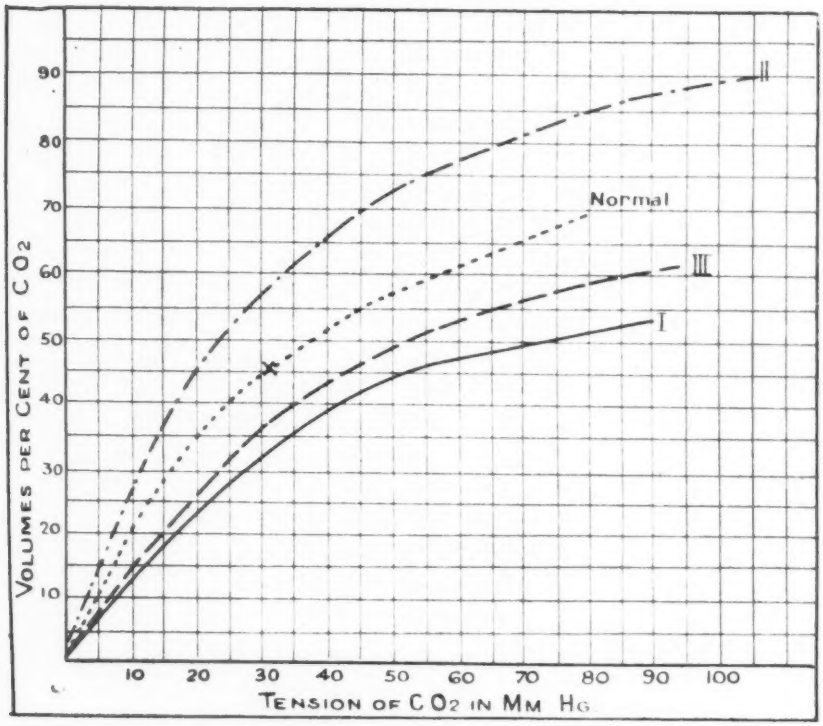
adults. Such, however, was not our experience in this series. Straub, Meier and Schagintweit[6] found that there was a greater variation in the CO_2 dissociation curves in Germany during the hunger years 1917 to 1919 than in 1921, and they attributed this directly to the poor nutritional conditions leading to an unstable acid-base equilibrium.

SIGNIFICANCE AND DISCUSSION OF ABNORMAL CURVES.

It must be emphasized at this point that the direction of the deviation of the curve from the normal does not determine whether there is a state of acidosis or alkalosis. An increase in the CO_2 capacity may be due to a primary decrease in the non-gaseous acid radicles such as Cl, PO_4, etc. (non-gaseous alkalosis), or to an increase in the CO_2 which has led to a secondary migration of these non-gaseous acid radicles (gaseous acidosis). Similarly a decrease in the capacity

of the blood to hold CO_2 may be due either to a primary increase in the non-gaseous acid radicles (non-gaseous acidosis), or to a primary decrease in the CO_2 (gaseous alkalosis). *Thus, by itself, a CO_2 dissociation curve does not give any more information about the pH of the blood than can be determined by a single determination of its total CO_2 content.* If, however, in addition to the dissociation curve, the total CO_2 content of the arterial blood be known, a figure representing the pH of that sample of blood can readily be ascertained. For example, the CO_2 dissociation curve of a sample of blood is as shown in Fig 3 (normal curve). The total CO_2 content of the arterial blood in this case was 45 vol. per cent.

FIG. III.



I Salicylate poisoning.
II Pyloric stenosis.
III Lobar pneumonia.

Therefore the tension of CO_2 necessary to enable the blood to take up 45 vol. of CO_2 is 31 mm. Hg. This point marked x on the graph (Fig. 3) is known as the arterial point. By means of Bohr's coefficient of solubility for CO_2 in whole blood (0·51), the tension is equivalent to 2·08 vol. per cent., which represents the free CO_2 content of the blood. The combined CO_2 is then 42·92 vol. per cent. (45·0—2·08). Hasselbalch's formula $pH = pk_1 + \log \frac{[BHCO_3].}{[HCO_3]}$ pk_1 being a constant equal to 6·1— can now be used to determine the pH, which is thus equal to $6{\cdot}1 + \log \frac{42{\cdot}92}{2{\cdot}08}$, i.e., 7·415.

It is still under discussion whether the dissociation curve determined from fully oxygenated venous blood gives a correct picture of the conditions in arterial blood. Acid substances are produced by the tissues especially during work, and lower the CO_2 combining capacity of the blood. These acid substances, however, are not given off in the lungs but are carried over into the arterial system. Eppinger and Schiller[7] have shown that the CO_2 curves of arterial and venous blood differ but little, such differences as there are being well within the limits of experimental error, but Fraser, Graham and Hilton[8] maintain that such is not the case in the majority of cases. It must be admitted that in disease, where there may be pathological conditions such as a marked relative increase in the corpuscular volume of venous blood, the CO_2 curves of arterial and venous bloods may show marked differences.

If the total CO_2 content of the blood has been determined from a venous sample there will be introduced an error in the determination of the pH owing to the fact that venous blood contains 2 to 4 volumes of CO_2 more than the arterial, the exact amount depending roughly on the degree of venosity. The figure derived from the venous CO_2 and the dissociation curve indicates the pH neither of the arterial nor of the venous blood. To obtain the venous pH it would be necessary to construct a CO_2 dissociation curve at the tension of oxygen which is present in the venous blood. Despite this error the figure obtained by using the CO_2 content of the venous blood and the CO_2 dissociation curve of fully oxygenated blood does yield a figure which is of some value in assessing the state of the acid-base balance.

The curves obtained from the bloods of three children suffering from conditions in which it appeared probable that there was some disturbance in acid-base balance are given in Fig. 3.

Curve I was obtained from the blood of a child suffering from salicylate poisoning. The curve is shifted to the right of normal and is thus hypocapnic. This might be due either to the over-production of acid substances such as occurs in diabetic coma with the consequent diminution in the available alkali (non-gaseous acidosis), or to the over-stimulation of the respiratory centre with washing-out of the CO_2 by over-breathing (gaseous alkalosis). The total CO_2 content of the venous blood was 32·4 vol. per cent.; by using this figure in conjunction with the dissociation curve (admittedly an inaccurate method for reasons already given) we find that the pH is 7·28 which is to the acid side of normality.

Curve II was obtained from the blood of an infant with congenital pyloric stenosis. It is to the left of normal (hypercapnic). This might be due either to a diminution of the acid radicles (non-gaseous alkalosis), or to depression of the respiratory centre with decreased output of CO_2 (gaseous acidosis). The volume of breathing would be diminished in both conditions. In the first instance (non-gaseous alkalosis), the combined CO_2 is primarily increased and the breathing would be diminished in an effort to keep the free CO_2 as high as possible and so cause a minimal disturbance to the normal $HCO_3 : BHCO_3$ ratio of 1 : 20. In the case of the gaseous acidosis, the primary change is in the free CO_2 which is conserved because of the diminished sensitivity of the

respiratory centre by some poison or toxin (morphine). The combined CO_2 is secondarily raised in order to keep the ratio as constant as possible. The work of other investigators as well as some unpublished work of our own shows that in pyloric stenosis, the pH of the blood is frequently on the alkaline side of normality. This indicates that the hypercapnic nature of the CO_2 dissociation curve in this condition is due to a diminution of the acid radicles, that is, a non-gaseous alkalosis. It must be emphasized that such a conclusion is not justified by a consideration of the dissociation curve alone.

Curve III is the curve obtained from the venous blood of a boy on the fourth day of a lobar pneumonia. The curve is hypocapnic and the total CO_2 content of the venous blood was slightly diminished, namely 43·3 vol. per cent. On the curve the CO_2 tension at this volume of CO_2 is 40 mm. Hg. which is the equivalent of a free CO_2 content of 2·69 vol. per cent. The combined CO_2 would then be 40·61 vol. per cent., and by applying Hasselbalch's formula, the venous pH works out at 7·27. As this patient was seven years old, it was possible to obtain the figure for the free CO_2 in another way, namely by the analysis of air equilibrated with the arterial blood in the rectum. By this method the tension of CO_2 was found to be 37·7 mm. Hg. the equivalent of 2·53 vol. per cent. Employing this figure, the combined CO_2 would be 40·77 vol. per cent., and the pH 7·29 which is more accurate than the venous pH of 7·27. It is of interest to note that on the curve at a tension of 37·7 mm. Hg., the total CO_2 is 42 vol. per cent., whereas that determined in the venous blood was 43·3 vol. per cent.

These figures suggest a mild degree of non-gaseous acidosis. One must, however, be cautious about drawing conclusions. Oxygen desaturation of varying degree is always present in lobar pneumonia and must be taken into account in a consideration of the state of the acid-base balance. Meakins and Davies[9] believe that the condition usually present in lobar pneumonia is a partially compensated gaseous alkalosis. Such a condition would of course, also shift the CO_2 dissociation curve to the right, *i.e.*, render it hypocapnic and cause a diminution in the total CO_2 content as occurred in this case. At the same time lobar pneumonia is usually associated with a markedly acid urine and an increase in the excretion of ammonia. There is a retention of chlorine, which is not, however, evidenced by a high blood chloride content. In addition an increase in some unknown organic acid radicle has been reported in the blood. All these facts tend to support the view that the condition is an acidosis. On the other hand Binger, Hastings and Neill[10] have reported a case in which the administration of sodium bicarbonate had a distinctly harmful effect by producing a marked alkali excess in the blood, although the urine remained acid throughout. Another factor of importance is the anoxæmia which *per se* induces an alkalosis. Many years ago, Bohr, Hasselbalch and Krogh[11] demonstrated that lowered tensions of CO_2 caused the oxyhæmoglobin dissociation curve to shift to the left, that is to hold on more firmly to its oxygen. It is difficult, therefore, to reconcile the association of the diminished oxygen saturation with a condition of alkalosis. It must be admitted that the question is one of extreme complexity, and it cannot be finally decided from the findings so far obtained.

Conclusions.

1. The limits of the CC_2 dissociation curves obtained from the bloods of ten normal children at 40 mm. Hg. are from 47 to 56 vol. per cent. (−8·0 to +9·8 per cent).

2. Haggard and Henderson's observations on the occurrence of hæmolysis at low tension with consequent reduction in the CO_2 combining capacity are confirmed.

3. The CO_2 dissociation curve in one case of pneumonia and one case of salicylate poisoning is shown to be hypocapnic and in one example of pyloric stenosis to be hypercapnic. The significance of these findings with reference to acid-base equilibrium is briefly discussed.

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THE CARDIAC CLINIC AND HOSPITAL—THEIR VALUE IN THE CONTROL OF THE RHEUMATIC INFECTION.

BY

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Within recent years there has been much discussion of the care of the rheumatic child. This has resulted in great part from our altered attitude to the pathology of rheumatism. The modern conception of rheumatism is that it is a chronic infection akin to tuberculosis. After the contagium vivum—whatever its nature—gains entrance to the body it lingers for long periods, dormant perhaps at times but with a great tendency to light up every now and again. Hence it is no longer considered sufficient to treat the acute manifestations as they arise, or right to look upon the disease as cured after their subsidence, but that for a long time afterwards treatment should be continued and a close watch kept for the development of a recrudescence. So far as the hospital class is concerned, and it is this class which provides the vast majority of our examples, this supervision may be carried out while the child is still at home through periodic visits to an out-patient clinic or by having him resident in a special hospital set apart for the purpose.

These out-patient clinics are variously named 'cardiac clinics,' 'rheumatic clinics' or 'rheumatism supervisory centres' and in spite of the writings of some of our English colleagues, they are all, whatever their designation, endeavouring to do the same work, namely, the avoidance of recurrences of the rheumatic infection and especially the avoidance of the development of cardiac disease. It was to focus attention on the latter—the gravest and really incapacitating manifestation of the infection—that the name 'cardiac clinic' was employed, and in our opinion there is much merit in its selection.

The special hospital for cardiac or rheumatic cases has the great advantage of removing the child from the predisposing environment. It has been remarked upon by most writers on rheumatism, at least so far as children are concerned, that it exacts its toll from the poorer, though not the poorest, classes of society. This would indeed seem to be one of the most definite facts about the disease. While examples of the condition are never wanting among one's hospital clientele they are of the rarest occurrence in private practice. This strongly suggests that environment is a most important factor in its causation, a conclusion which is supported by the varying incidence of the disease among the same class of child when resident at home and when resident under good conditions, *e.g.*, in orphan homes. This was brought out in a striking manner by Dr. Benjamin[1] in his contrast of the frequency of the disease in children while resident in Poor Law Schools of London and in their own homes.

It is advisable that these special cardiac hospitals, not only for purposes of health but also for purposes of economy, be situated in the country. It must be perfectly understood, however, that they must be, at least if they are intended for the child the subject of cardiac disease, different from the ordinary convalescent home. It is necessary that the child be kept under strict medical supervision and it is advisable, considering the age of the patients and the duration of residence, that facilities be provided for the children to proceed with their education. These hospitals must be of the same type and staffed as those provided for surgical tuberculosis and orthopædic cases.

Though there have been for some years now facilities for the after-care of the rheumatic child in this country the work was only carried out in a half-hearted fashion and it was left to our American colleagues to take it up in their usual thorough manner. In most centres in America clinics for the continued after-care of rheumatic children have been instituted and are now part and parcel of pædiatric departments. It is perhaps to St. Lawrence of New York, however, that we are indebted for most stimulation.

Reports emanating from New York and other centres in U.S.A., but especially from the pen of St. Lawrence[2], stressed the benefits to be obtained from the after-care of both children and adults suffering from rheumatism and stimulated us to inaugurate in 1923 a cardiac clinic at the Royal Hospital for Sick Children, Glasgow, so that all examples of rheumatism admitted to the wards could be continuously supervised after their dismissal. This we believe was the first of its kind in this country. We had, however, only very limited accommodation for the prolonged in-door treatment of the cases until one year ago, when, through the generosity of an anonymous donor, we were provided with facilities for accommodating 12 children.

Since 1923 the routine practice in the treatment of the rheumatic child at the Royal Hospital for Sick Children, Glasgow has been as follows. All children admitted with chorea or arthritis, or other active manifestation of the rheumatic infection, are kept in bed for at least three months, as much, if not more attention being paid to the cases with early manifestations and the heart still intact. During their residence they are given a full course of salicylate, and advantage is taken of the opportunity to have the tonsils enucleated, and to have the teeth attended to whenever there is the least suspicion of disease. If the mischief seems quiescent at the end of the three months in bed the child is gradually allowed up, the daily amount of exercise being regulated by the behaviour of the pulse, and in a matter of 10 days or so he is sent for a period to a convalescent home. After returning to his own home the child reports periodically at the Cardiac Clinic, the frequency of the visits being governed by the necessities of the case. Some patients attend every fortnight while others again may only require supervision every two or three months. During this attendance at the clinic the children are given periodically courses of salicylate—two months on and two months off—teeth and throat are attended to, re-admission to Hospital or transfer to a convalescent home provided for as required, clothing and home conditions not being neglected and remedied

where possible. Careful notes are kept of the progress of the disease and we have now in consequence details of the history of some patients extending over as long a period as eight years.

The present communication is a record of our experience with these various facilities. In the first place we will deal with the results obtained at the cardiac clinic as these extend over the longest period—now five years. We have selected as the material for analysis those cases which first came under observation during the years 1922-1924 inclusive. This means that those attending the clinic had been under continuous supervision for a matter of five years, which we consider quite ample to enable us to judge whether or not the method is of any real value in combating the progress of the disease.

A certain number of our rheumatic children, either through lack of interest on the part of the parents or for other reasons, never did attend the clinic, and as many of these as possible were traced in 1928, their intervening histories obtained and their present condition observed. These cases which we call non-clinic cases have been used for comparison with the clinic cases. Thus we have a group of cases supervised and another group not supervised. It must be admitted that the comparison is not absolute since a certain number of the non-clinic cases who could not be traced may have died and others may have been too ill to appear at the hospital for examination, and hence the results relative to these non-clinic cases may appear better than they really are, but such a group is the only possible one we have available for our purpose.

There were 52 non-clinic children and 80 clinic children, and so far as recurrences of the disease are concerned it was found that there were fewer per person during the post-hospital period among the non-clinic than among the clinic cases (Table 1).

TABLE 1.

SHOWING CASE-INCIDENCE OF RHEUMATIC ATTACKS IN CLINIC AND NON-CLINIC CHILDREN.

Group.	Total No.	Attacks before adm. to hospital.	Average attacks per person.	Attacks after dismissal.	Average attacks per person.	Total no. of attacks.	Average attacks per person.
Non-clinic children ...	52	74	1·42	22	·41	96	1·8
Clinic children ...	80	121	1·53	42	·60	163	2·03

It will be readily understood that the parents of all the children would not co-operate equally well in this after-care and for a further analysis we have subdivided the clinic group according to whether the attendance was good, fair or bad (Table 2). Of these clinic children the highest incidence of recurrences was obtained among those cases who attended most regularly. The numbers are admittedly small but they certainly do not, any more than the comparison of the clinic and non-clinic cases, offer proof that regular attendance at the clinic, and continuous after-care of the rheumatic child, are any real protection against further attacks of the rheumatic infection.

TABLE 2.

SHOWING CASE-INCIDENCE OF RHEUMATIC ATTACKS IN THE CLINIC CHILDREN ACCORDING TO REGULARITY OF ATTENDANCE.

Group.	No. of cases.	Attacks before admission to clinic.	Attacks after admission to clinic.
Good attendance	45	71 = 1·58 per case	30 = ·66 per case
Fair „	12	17 = 1·4 per case	3 = ·25 per case
Bad „	23	34 = 1·48 per case	8 = ·34 per case

We have already remarked that the dominating factor in the rheumatic infection is the presence of cardiac disease. It was indeed for the prevention of this complication, or for its amelioration, that these clinics were instituted and hence it is of prime interest to follow the course of events in those children who had been satisfactorily supervised, and see if our efforts in this direction had been in any way rewarded. For the purpose of our analysis again the clinic and non-clinic children have been contrasted as well as those attending well, fair or badly with one another.

In the following table (Table 3) is shown the development of cardiac disease in the clinic and non-clinic cases during the post-hospital period—*i.e.*, the 5

TABLE 3.

SHOWING DEVELOPMENT OF CARDIAC DISEASE IN CLINIC AND NON-CLINIC CASES.

Group.	No. of cases.	Condition of heart on dismissal from hospital.	Condition on admission to clinic.	Condition in 1928.	Remarks.
Clinic children ...	80	40 − 40 +	40 − 40 +	35 −; 5 + 27 +; 11 − (2 died).	12% developed cardiac disease during attendance at clinic. 27% lost murmurs.
Non-clinic children	48	23 − 25 +	− −	19 −; 4 + 17 +; 5 − (3 died)	21% developed cardiac disease. 20% lost murmurs.

+ = Evidence of heart disease.
− = No evidence of heart disease.

years that the clinic has been in existence. These results show a slight but definite advantage in favour of the clinic cases, as only 12 per cent. of the clinic cases developed murmurs as against 21 per cent. of the non-clinic cases. It is interesting to note too that during the period of observation 27 per cent. of the clinic cases lost the cardiac murmur, whereas this happened in only 20 per cent. of the non-clinic cases. These latter murmurs were probably in the majority of instances due to myocarditis.

This benefit from attendance at the clinic would seem, however, to be more apparent than real as it is completely counterbalanced by the behaviour of the cardiac condition when related to the regularity of attendance. In Table 4 it is seen that the proportion of cases which improved is highest in those who attended least regularly and that the proportion of those who deteriorated was highest among those who attended best.

TABLE 4.

SHOWING PROGRESS OF CARDIAC DISEASE IN CLINIC CASES ACCORDING TO REGULARITY OF ATTENDANCE (1924—1928).

Group	No. of cases.	Progress	
Good attendance	45	improved	4 = 9%
		I.S.Q.	35 = 78%
		deteriorated	6 = 13%
Fair attendance	12	improved	3 = 25%
		I.S.Q.	8 = 66%
		deteriorated	1 = 9%
Bad attendance	23	improved	4 = 17%
		I.S.Q.	18 = 78%
		deteriorated	1 = 4%

Thus from a review of the progress of events during the period of the child's attendance at the clinic there is little evidence that any great benefit was obtained. Recurrences of infection, at least so far as the arthritic and and choreic manifestations are concerned, were in no way prevented and the evidence of the slightly lower incidence of cardiac disease developing among the clinic than in the non-clinic cases was neutralised by the evidence of most satisfactory progress being observed among those children whose attendance at the clinic was least satisfactory. It may be of course that attendance at the clinic was in great part dependent on the necessity of the child for treatment, *i.e.*, so long as the child kept well the parents, not seeing any need for medical advice, did not attend and in fact only did so when a recurrence of the mischief ensued or when the child's cardiac condition was deteriorating and causing increasing embarrassment.

Let us now consider the progress of these cases transferred to the Cardiac Hospital in the country. The hospital is situated about 7 miles beyond the city boundaries and is built in pavilion style. The education authorities have put at our disposal a mistress who visits daily and gives instruction to those children who are considered well enough to benefit from it. Here, as we have remarked, there are facilities for accommodating only 12 children and as it is just a year since the beds were available the material for analysis is small. During the year, however, there have been under observation 14 children with an average residence of 40·5 weeks per child. Only one patient has presented during the year any active rheumatic manifestation, namely, a recurrence of chorea. Otherwise the children have been remarkably well and most of them

have proceeded with their education. It would of course be ridiculous to express arithmetically the facts relative to this small series, but it may be said that the incidence rate of rheumatic manifestations is only half of that which prevailed among the children attending the out-patient clinic at the Hospital, so that by this means some benefit would seem to have been obtained. Records from a similar institution in connection with St. Louis Children's Hospital[3], U.S.A., which has been in operation for two years, also reveal a less incidence of attacks during residence, but unfortunately after their return home a greater incidence than occurred among children who had never been absent at all from their homes. It would seem as if in consequence of their removal to healthier surroundings the children had lost a certain amount of their immunity and become more susceptible to the disease.

Such then is the record of our attempt to control the ravages of the rheumatic infection and it must be admitted that it does not engender a feeling of optimism. We can only conclude that the cardiac clinic—at least as an out-patient department—is of very little if any avail, and even the cardiac hospital in the country, unless perhaps as a permanent residence, would seem to be little more effective. In any case most people will agree that the results are not commensurate with the energy expended, and certainly fall short of what would have been anticipated.

It may be suggested in criticism that we could not expect more when we select cases in which the disease is well advanced and it will be recommended that we concentrate on what is called the pre-rheumatic child. But we ask, how can we recognize him ? To us there is nothing more nebulous in medicine than what is spoken of as the pre-state of a disease. We know that the descendants of a rheumatic stock are specially susceptible to the infection, just as we know that the descendants of a stock with examples of muscular dystrophy are specially liable to the development of this disease, but how can we recognize the individual who is going to contract rheumatism or whose muscles are to degenerate prematurely ? The pre-state, just as the so-called diathesis, is an early or mild form of that disease. By all means let us try and discover the earliest manifestation of the malady so that we may as soon as possible be on the defensive, but let us not make the clinical picture of this early phase so all-embracing as to make the whole world suspect.

If, however, it would seem impossible either to cure or control the disease when it has appeared, is it possible to prevent it ? The moral of our experience in Glasgow is we believe to concentrate on prophylaxis. Although we do not know the cause of the disease, we do know that it exacts its toll from the poorer classes of the community, and that the housing conditions of these rheumatic families is often most insanitary. They are damp and low lying and sunless. The almost complete immunity of the same class of child when resident under good conditions in the London County Council orphan homes, and the comparative immunity of the better classes, admit of no other conclusion than that at present change of environment is our chief weapon. The experience of Drs. McCulloch and Irvine-Jones that after a temporary improvement in environment the susceptibility of the individual becomes increased would

indicate that this change of environment, however, should be a permanent one. This spells nothing short of housing reform. The sequelæ of rheumatic fever are fast usurping the place held by tuberculosis in the past among the chief causes of death, and the lessons of our work in Glasgow in an attempt to fight rheumatism are a further incentive, if any were needed, to the provision of healthy homes for the poorer classes of the community.

Conclusions.

1. Regular supervision at a cardiac or rheumatism out-patient clinic does not seem to diminish the recurrences of the rheumatic infection.
2. Regular supervision at a cardiac or rheumatism out-patient clinic does not seem to affect markedly the progress of rheumatic heart disease.
3. Residence in the country under medical supervision does seem to control the rheumatic infection.
4. As the rheumatic infection cannot be controlled to any great extent chief attention should be directed to prophylaxis.
5. Modification of environment is at present our chief prophylactic weapon and means provision of healthy homes for the poorer classes of the community.

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TONSILLECTOMY IN THE PREVENTION AND TREATMENT OF RHEUMATISM.

BY

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In the organized attack on the rheumatic infection there is probably no more debated point than that of the efficacy of tonsillectomy. As portals of entry of the virus the tonsils are supposed to occupy first place, and hence it is only natural that one of the commonest procedures in the attempt not only to prevent the disease but also to hinder its progress, should consist in their removal. It must be admitted, however, that so far as the latter purpose is concerned the operation savours of locking the stable after the steed has been stolen.

Statistics vary regarding the incidence of disease of the tonsils in examples of the rheumatic infection, but there is no doubt that in a goodly proportion of the patients abnormal tonsillar tissue is present and that a history of a previous tonsillitis is obtained. In a recent survey in London[1] the incidence of diseased tonsils in rheumatic children was said to be roughly 60 per cent. as against 50 per cent. in non-rheumatic children, whereas in a simultaneous enquiry carried out in Glasgow only 45 per cent. of the rheumatic and 40 per cent. of the non-rheumatic presented tonsillar abnormality. Disease of the tonsils is thus so widespread, not only among the non-rheumatic members of the class of society which provides the majority of our examples of rheumatism, but as we all know among the children of the better classes as well, in whom on the other hand, rheumatic fever is admittedly rare, that it is exceedingly difficult to assess the importance of this condition in the pathogenesis of the infection. Nevertheless it seems rational to remove a possible focus of infection and portal of entry, apart altogether from the effect of the operation on the general health, and it has been our custom to have the tonsils enucleated in all examples of the disease when there was any question of enlargement. The present communication is an analysis of our results in an attempt to appraise the value of this line of attack.

Effect of tonsillectomy on arthritis and chorea.

Much work has already been done in this direction and an enormous literature has grown round the question of tonsillectomy and its effects. At first the reports of the result of the operation were laudatory but latterly they have revealed much scepticism. Miller[2], however, raises an interesting and possibly important point in the issue when he differentiates between chorea and arthritis in assessing the value of this operation, and in the analysis of our material we have followed his example. Thus in Table 1 arthritis and chorea have been classified separately so that the effect of the operation on these two manifestations may be contrasted. In addition, however, the effect on the rheumatic infection as a whole is shown by not differentiating between the

types of manifestations (Table 2). The number of attacks include not only initial attacks but all recurrences as well.

It will be readily understood that to judge properly of the value of the operation of tonsillectomy it is essential that the cases be observed over a prolonged period and hence we have selected those cases which first came under our notice during the years 1922-1924 inclusive. The cases had been followed during the succeeding years and all were seen towards the end of 1928. This material comprises a total of 153 patients from which to draw conclusions. In contrasting the various groups it should be noted that all the patients were under observation for approximately the same length of time, namely, 5 to 8 years, and as the operation was performed in the great majority of the cases prior to 1925, the pre- and post-tonsillectomized-observation periods are also approximately of the same duration.

TABLE 1.

SHOWING EFFECT OF TONSILLECTOMY ON ARTHRITIS AND ON CHOREA.

Group.	Arthritis			Chorea		
	No. of cases.	No. of attacks.	No. per person.	No. of cases.	No. of attacks.	No. per person.
Tonsillectomized before first attack	3	5	1·7	7	21	3·0
Not tonsillectomized.						
(*a*) Requiring tonsillectomy ...	36	49	1·3	16	12	0·7
(*b*) Not requiing tonsillectomy	32	51	1·6	19	34	1·8
Total ...	68	100	1·5	35	46	1·3
Tonsillectomized during observation	27			24		
Before		32	1·2 } 1·4		33	1·3 } 1·96
After		7	·2 }		6	·66 }

In Table 1 perhaps the most striking feature is the smallness of the group of cases developing arthritis after a preliminary tonsillectomy. This fact is particularly arresting when one appreciates that of the total 153 cases investigated patients with arthritis were half again as numerous as those with chorea numbering as they did 90 and 63 respectively. At first sight this altered proportion of arthritis to chorea might seem to give some support to Miller's contention that tonsillectomy has a greater prophylactic effect on arthritis than on chorea, if it has any prophylactic effect at all, yet a survey of the state of matters which prevailed in the non-tonsillectomized children reveals a less incidence of attacks per person of both chorea and arthritis and among these a greater incidence in those who did not require tonsillectomy. Hence one feels rather dubious about drawing any conclusions. The same points too emerge from the analysis of all the cases when no differentiation is made between the types of the rheumatic manifestation, viz :—a greater incidence of manifestations per person among the tonsillectomized than the non-tonsillectomized and among the latter a greater incidence in those not requiring the operation than in those who did (Table 2).

TABLE 2.

EFFECT OF TONSILLECTOMY ON RHEUMATIC MANIFESTATIONS.

	No. of cases.	No. of attacks.	No. per person.
Tonsillectomized before first attack	8	21	2·6
Not tonsillectomized.			
(*a*) Requiring tonsillectomy	45	82	1·8
(*b*) Not requiring tonsillectomy	42	82	1·9
Total	87	164	1·8

It may be, of course, that of children the subjects of a preliminary tonsillectomy it is only the specially susceptible who will succumb, and in them recurrences would naturally tend to be more numerous. This hypothesis gains support from the behaviour of the rare examples of the disease in the better class child, who from the family history would seem specially susceptible and who, in spite of extreme care and living under ideal conditions, runs through the whole gamut of the malady within a comparatively short time.

In Table 1 are also detailed the number of attacks for the periods before and after the operation in these cases submitted to tonsillectomy during the course of the infection. As the ante- and post-operation periods are on the whole shorter—on the average only one half of the total period of the disease observed—one would not expect the same case incidence. Moreover, as there would always be a greater number of 1st attacks then 2nd attacks, and 2nd attacks than 3rd attacks and so on, and as the tonsillectomy was always performed after the disease had disclosed itself by the presence of one or more attacks, there would be a natural tendency for the case incidence to be less high during the post-operation than during the pre-operation period. This is in fact what was found. The figures do show, however, that there was a greater fall during the post-operation period in the incidence of arthritis than of chorea, but it is very questionable if any conclusions can be drawn from this difference since the sum of attacks, at least in arthritis, during the two periods—ante- and post-operation—practically equals the incidence found during the whole course of the illness in the non-tonsillectomized patients.

Thus though a preliminary tonsillectomy may possibly render an individual less susceptible to arthritis, our results do not lend any support to the idea that an intercurrent tonsillectomy prevents recurrences of either arthritis or chorea. In this connection it is worth remembering, however, that as cardiac disease is more likely to follow arthritis than chorea, any benefit of a preliminary tonsillectomy in preventing arthritis will assume an added value.

EFFECT OF TONSILLECTOMY ON THE DEVELOPMENT OF CARDIAC DISEASE.

Even supposing, however, that tonsillectomy does not make an individual less susceptible to arthritis or chorea, is it possible that it might render less

probable implication of the heart ? This is a statement which has indeed been made by several writers, *e.g.*, Kaiser[3] and Miller[2].

In a study of this question we have come to the conclusion that it is important to distinguish between an initial or preliminary tonsillectomy and one performed during the course of the illness, since on the particular stage of the disease depends the probable development or otherwise of disease of the heart. There would seem to prevail a certain amount of doubt regarding the period in the course of the disease at which carditis is most probable, and whether or not recurring arthritis or chorea renders an individual more liable to this complication. In order to obtain evidence on this point it is essential that the complete history of the infection be known so that the cardiac implication can be related to a particular rheumatic attack. Any case coming under observation with a cardiac lesion and having already passed through several attacks of chorea or arthritis is unsuitable for the purpose, but those patients who were seen with the first manifestation of the disease, or those with a history of one or more attacks, and with the heart still intact, are applicable. Of such suitable cases for analysis we have 108.

In the following table (Table 3) where the cases are grouped according to whether there occurred in the one individual both chorea and arthritis, or only chorea or arthritis, the number of patients passing through one or more attacks and the percentage incidence of cardiac disease consequent on each attack are shown. It should be noted that the cases included in any succeeding subgroup are only those who had passed through a previous attack with the heart unscathed.

TABLE 3.

SHOWING THE INCIDENCE OF CARDIAC DISEASE DEVELOPING IN 1ST, 2ND OR 3RD, ETC., ATTACK OF ARTHRITIS AND CHOREA.

	No. of cases.	No. developing cardiac disease.
A. *Arthritis alone* (56 cases).		
1st attack...	56	24 = 43%
2nd ,, ...	2	2 = 100%
B. *Chorea alone* (36 cases).		
1st attack...	36	11 = 30·5%
2nd ,, ...	13	6 = 46·0%
3rd ,, ...	3	0
4th ,, ...	2	0
5th ,, ...	2	0
C. *Arthritis and Chorea* (16 cases).		
1st attack...	16	10 = 62%
2nd ,, ...	6	1 = 16%
3rd ,, ...	1	0
4th ,, ...	1	0
5th ,, ...	1	0

From the above analysis it is seen that in no case in which the time of appearance of the cardiac involvement was known did this complication develop after the 2nd attack. This was so not only in those patients with chorea or arthritis alone, but also when they suffered from both chorea and arthritis. In this last group the onset of heart disease was related, as previously mentioned, to the rheumatic manifestation in its true sequence, whether such was chorea or arthritis. In the cases with arthritis or chorea there was a greater incidence of cardiac disease during the 2nd attack than during the first, in fact every case of pure arthritis which escaped carditis during the 1st attack succumbed during the second. In the cases with both arthritis and chorea there was, on the other hand, a greater incidence during the 1st than during the 2nd manifestation of the disease. Without doubt the number of cases of arthritis passing through a second attack is too small to warrant serious consideration, but the other groups of cases are sufficiently large to justify at least tentative conclusions. It would seem, therefore, so far as the evidence of our material goes, that if carditis is to result it will do so during the 1st or 2nd attacks of arthritis or chorea, and on the whole is more likely to develop during the 2nd than during the 1st, but seldom if ever after an individual has passed through two attacks with the heart unscathed. This relationship of carditis to the first or at least the early attacks of arthritis or chorea, in addition to having a comforting prognostic significance, focusses attention on the importance of prophylaxis. The chief point, however, in connection with these findings, so far as the present discussion is concerned, is that if we wish to draw deductions regarding the effect of tonsillectomy on the prevention of cardiac disease only those cases which were tonsillectomized before the onset of the disease, or before the 2nd attack of chorea or arthritis, and of course with the heart still intact, can be legitimately contrasted with the non-tonsillectomized examples. This comparison is shown in the following table (Table 4). The non-tonsillectomized cases are considered not only as a whole but also according to whether tonsillectomy was or was not considered necessary.

From Table 4 it is seen that of the cases with chorea alone the least incidence of cardiac disease was in those who were the subjects of a preliminary tonsillectomy. This apparent benefit of tonsillectomy is, however, counter-balanced by the fact that there occurred a greater incidence among those tonsillectomized early in the course of the disease than among those never tonsillectomized.

In the cases with arthritis alone the one child who was operated upon before the occurrence of any rheumatic infection escaped altogether affection of the heart, and there was also a very low incidence in those tonsillectomized early in the disease. Of the non-tonsillectomized cases, however, the less incidence occurred in those requiring tonsillectomy, so that the highest incidence of cardiac disease among the children with apparently normal throats is the most noteworthy feature of this group.

Of those children who suffered from both arthritis and chorea a greater incidence of cardiac disease was obtained in the tonsillectomized, and among the non-tonsillectomized the frequency of cardiac involvement apparently bore no relationship to the need of the operation.

TABLE 4.

SHOWING EFFECT OF TONSILLECTOMY ON DEVELOPMENT OF CARDIAC DISEASE.

		No. of cases	No. with cardiac disease	% with cardiac disease
A.—Cases with chorea alone.	Non-tonsillectomized.			
	(*a*) Requiring tonsillectomy	9	3	33
	(*b*) Not requiring tonsillectomy ...	10	2	20
	Total	19	5	26
	Tonsillectomized: before infection ...	6	1	16·6
	,, : before 2nd attack ...	6	3	50
B.—Cases with arthritis alone.	Non-tonsillectomized			
	(*a*) Requiring tonsillectomy	30	16	53
	(*b*) Not requiring tonsillectomy ...	25	16	64
	Total	55	32	58
	Tonsillectomized: before infection ...	1	0	0
	,, : before 2nd attack ...	8	1	12
C.—Cases with chorea and arthritis.	Non-tonsillectomized.			
	(*a*) Requiring tonsillectomy	7	4	57
	(*b*) Not requiring tonsillectomy ...	9	5	55
	Total	16	9	56
	Tonsillectomized: before infection ...	1	1	100
	,, : before 2nd attack ...	3	2	66
D.—All cases ...	Non-tonsillectomized.			
	(*a*) Requiring tonsillectomy	52	28	53·8
	(*b*) Not requiring tonsillectomy ...	46	25	54
	Total	98	53	54
	Tonsillectomized: before infection ...	8	3	37
	,, : before 2nd attack ...	15	5	33

When all the cases are grouped together, irrespective of whether they suffered from arthritis or chorea, a less incidence of cardiac disease is seen among the tonsillectomized but of the non-tonsillectomized there was no difference when classified according to evidence of disease of the tonsils.

The findings then are so various and contradictory that it is very difficult, in fact impossible to draw any conclusions. Some of the groups of course are too small to warrant any consideration at all, and it is possible that with a much larger series of cases some more definite evidence one way or the other might be forthcoming. The apparent benefit of tonsillectomy in the case of those patients who suffered from arthritis alone is negatived by the findings in those suffering from chorea, as also by the greater susceptibility of those requiring tonsillectomy among the non-tonsillectomized group. The possible beneficial effect of tonsillectomy in preventing cardiac disease in the arthritic group is, however, in keeping with the previously mentioned possible prophylactic effect on arthritis of a preliminary tonsillectomy, but the whole evidence is so slight that one hesitates to formulate any generalisation for or against this line of attack.

Effect of tonsillectomy on the progress of the cardiac condition.

Even although the operation of tonsillectomy has no marked effect in hindering the development of disease of the heart it might be that it would have some influence on the progress of the disease, and the analysis of our material relative to this point is given below (Tables 5, 6 and 7).

In our work at the cardiac clinic or rheumatism supervision centre it has been the custom to classify the cases according to the presence or absence of a cardiac lesion and according to the severity of this lesion when present, thus :—class P, (potential cardiac disease) cases with no cardiac disease ; class A, cases with a transient murmur during the acute phase ; class B, cases with signs but no symptoms of heart disease ; class C, cases with signs and moderate symptoms of heart disease ; class D, cases with signs and marked symptoms of heart disease. For a fuller appreciation of the progress of the cardiac condition during the period under consideration the classification on dismissal from hospital (1924) and that on the occasion of the last examination (1928), as well as the direction in which the change of class occurred, are detailed in the Tables (Nos. 5, 6 and 7). As before, the cases have been grouped according to whether there was only chorea, only arthritis, or both arthritis and chorea in the one individual.

TABLE 5.

Showing progress of cardiac condition in tonsillectomized and non-tonsillectomized children.

Cases with chorea alone.

Class of case.	No. of cases.	Classification in 1924.	Change of class.	Classification in 1928.	% improved.	% deteriorated.
(*a*) Non-tonsillectomized.						
(1) Requiring tonsillectomy	9	4 P 5 B	3 P, 1 B 3 A, 2 B	3 P 3 A 3 B	33	11
(2) Not requiring tonsillectomy	10	8 P 2 B	8 P 1 A, 1 D	8 P 1 A 1 D	10	10
(3) Total	19	12 P 7 B	11 P, 1 B 3 B, 3 A, 1 died	11 P 3 A 4 B 1 dead	15·7	10·5
(*b*) Tonsillectomized before rheumatic infection	6	5 P 1 A	4 P, 1 B 1 A	4 P 1 A 1 B	0	16
(*c*) Tonsillectomized before 2nd attack ...	10	6 P 4 B	3 P, 3 B 3 B, 1 died	3 P 6 B 1 dead	0	40

TABLE 6.

SHOWING PROGRESS OF CARDIAC CONDITION IN TONSILLECTOMISED AND NON-TONSILLECTOMIZED CHILDREN.

CASES WITH ARTHRITIS ALONE.

Class of Case.	No. of cases.	Classification in 1924.	Change of Class.	Classification in 1928.	% improved.	% deteriorated.
(*a*) Non-tonsillectomized						
(1) Requiring tonsillectomy	30	6 P	5 P, 1 B	5 P	13	30
		5 A	5 A	9 A		
		12 B	7 B, 4 A, 1 died	8 B		
		1 C	1 died	8 dead		
		6 D	6 died			
(2) Not requiring tonsillectomy	25	5 P	5 P	5 P	12	25
		5 A	4 A, 1 B	4 A		
		6 B	6 B	10 B		
		3 C	1 B, 1 C, 1 died	1 C		
		6 D	4 died, 2 B	5 dead		
(3) Total	55	11 P	10 P, 1 B	10 P	13	25
		10 A	9 A, 1 B	13 A		
		18 B	4 A, 13 B, 1 died	18 B		
		4 C	1 C, 1 B, 2 died	1 C		
		12 D	10 D, 2 B	13 dead		
(*b*) Tonsillectomized before infection	1	1 P	1 P	1 P	0	0
(*c*) Tonsillectomized before 2nd attack ...	14	3 P	3 P	3 P	14	7
		4 A	3 A, 1 B	4 A		
		6 B	5 B, 1 A	7 B		
		1 C	1 B			

From the above analysis it is seen that of the cases with chorea alone the smallest proportion of cases deteriorated and the largest proportion improved among the non-tonsillectomized, and among these latter more satisfactory progress was observed in the case of those who required tonsillectomy. Of the cases with arthritis alone, on the other hand, if we except the small group of 2 the subject of a preliminary tonsillectomy, it was the non-tonsillectomized which showed the smallest proportion of improvement but the highest proportion of deterioration so that once more we see some slight evidence of the value of tonsillectomy when arthritis is the primary rheumatic manifestation. Of the cases with both chorea and arthritis those tonsillectomized showed the greatest proportion of deterioration and there was little difference in the incidence of improvement in the tonsillectomized and non-tonsillectomized. Thus on the whole we cannot discover any marked evidence of the beneficial effect of tonsillectomy.

TABLE 7.

SHOWING PROGRESS OF CARDIAC CONDITION IN TONSILLECTOMIZED AND NON-TONSILLECTOMIZED CHILDREN.

CASES OF ARTHRITIS AND CHOREA.

Class of case.	No. of cases.	Classification in 1924.	Change of class.	Classification in 1928.	% improved.	% deteriorated.
(*a*) Non-tonsillectomized	13	5 P 8 B	4 P, 1 B 3 A, 3 B 1 C, 1 died	4 P 3 A 4 B 1 C 1 died	23	23
(*b*) Tonsillectomized before rheumatic infection	1	P	B	B	0	100
(*c*) Tonsillectomized before 2nd attack	7	3 P 4 B	1 P, 2 B 2 A, 1 B 1 C	1 P 2 A 3 B 1 C	28	43

DISCUSSION.

A survey of the whole material above submitted supplies little evidence that tonsillectomy exerts any great effect on the development or course of the rheumatic infection. In view of some of the facts elicited, *e.g.* the small number of cases who develop arthritis after a preliminary tonsillectomy, the small proportion of cases of arthritis who have been tonsillectomized early during the course of the infection and who develop cardiac complications, and the tendency in these same cases for the cardiac condition to improve, it would seem that in the examples of the rheumatic infection characterized by arthritis rather than by chorea the operation may have both a prophylactic and a therapeutic effect. This possible beneficial effect assumes an increased importance when we remember that of all cases of rheumatic infection the majority are of the arthritic type, and that it is this type which is responsible for the greatest proportion of cardiac disease. The evidence, however, of the benefit accruing from the procedure is very slight and is counterbalanced by the less grave effects of the infection in those children not operated upon, but who apparently require it, than in those who are not the subjects of disease of the tonsils. In any case, if the operation is to be of any avail, so far as prevention of cardiac disease is concerned, it must be done before the onset of a second attack of arthritis as the heart would seem to be invariably implicated during either the 1st or second manifestation. In the case of those examples of the rheumatic infection characterized by chorea tonsillectomy would not seem to have any effect at all. This varying reaction to the effect of tonsillectomy

in the case of chorea and arthritis, as well as the fact that cardiac disease complicates much more frequently arthritis than chorea, raises the much discussed question of what proportion of examples of Sydenham's chorea are rheumatic in origin and suggests the possibility of a different strain of the infective agent in these two types of the disease.

We admit of course that our numbers are small, and it is quite possible that a larger series of cases might reveal more definite evidence one way or the other. The communication has the failings of its very virtues since by being the record of personal experiences in one clinic over a comparatively prolonged period the numbers are necessarily small.

Conclusions.

1. A preliminary tonsillectomy may possibly render an individual less susceptible to rheumatic arthritis but not to chorea.

2. A preliminary tonsillectomy or one performed early during the course of the infection may possibly, in the case of arthritis, render the heart less liable to be attacked but not so in the case of chorea.

3. As, however, cardiac complications usually ensue during the first or second rheumatic manifestations the operation to be prophylactic must be performed before the second attack.

4. Tonsillectomy in the case of carditis following arthritis seems to have a beneficial effect on the progress of the disease but not so in carditis following chorea.

5. The evidence in favour of the above beneficial effect of tonsillectomy in the case of rheumatic manifestations characterised by arthritis is, however, very slight.

6. The varying behaviour in response to tonsillectomy of examples of the rheumatic infection characterized by chorea and by arthritis suggests the possibility of a different strain of the infective agent in these two types of the disease.

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NON-TUBERCULOUS PLASTIC PLEURISY IN CHILDREN.

BY

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Spontaneous pleurisy occurring with or without an accompanying effusion in adults or in children, has always been considered to be more or less pathognomonic of active tuberculous disease. This communication presents two cases of proved non-tuberculous dry pleurisy in children.

Case 1. F. N., aged 6 years, was admitted to the East London Hospital for Children on February 5th, 1929, and was discharged on February 28th, 1929. She woke on the morning of the day of admission, crying out with pain in her left chest which was worse on deep inspiration. She vomited once. There was no cough. The bowels were open normally. The appetite had been good and there was no lassitude. There were no rigors and no delirium.

Past history. A full term, normal child; breast fed. She had had cervical abscesses at twelve months, diphtheria at thirteen months, pertussis and measles at three years, and bronchopneumonia on three different occasions.

Family history. Mother and father alive and well. Six other children alive and well. One, by the first wife, died of pulmonary tuberculosis.

On admission. Weight, 43¼ lb. Temperature 101°, pulse 120, and respirations 30. The child was well nourished and of a good colour. No herpes and no respiratory difficulty. Two healed scars were visible in the neck, where submaxillary abscesses had been incised. The tongue was furred. The tonsils were normal. Some lymphatic glands in the neck were palpable.

The chest examination on inspection and palpation was negative. The percussion note was normal over both lungs. On auscultation, a definite friction rub was heard over the left anterior chest and in the left axilla. A few fine râles were audible. There was no tubular breathing. The right chest, heart and abdomen were normal.

Course. Temperature, pulse and respiration fell to normal within two days. The rub disappeared in one week. She gained weight to 44¾ lb. on discharge. Throat and nose swabs were negative for diphtheria. Two test with old tuberculin (0·1 mgrm.) intradermally were definitely negative. X-ray of the chest was negative, showing no increased hilum shadows, calcified glands or other evidence of tuberculous infection. Blood examination showed leucocytes 9,800 (polymorphonuclears, 65 per cent., leucocytes, 35 per cent.). The urine was negative. Seen in the out-patient department on April 15th, 1929, her weight was 49 lb. There was no further pain or cough. The appetitie was good and the child was vigorous and healthy. She was again seen on June 21st, 1929. There were no symptoms. The weight was constant. Chest examination was negative. 1 mgrm. intradermally of old tuberculin gave a negative reaction.

Case 2. J. D., aged 7 years, entered the Hospital on March 14th, 1929, and was discharged on April 9th, 1929. He had had a slight cough for two weeks with the sudden onset of pain in the right lower chest two days before admission. This was worse on coughing and on deep inspiration. There was no vomiting. The bowels were open normally. Fever was present one day before admission. There had been no rigors and no delirium.

Past history. A full term, normal child; breast fed. Weight at birth was 7 lb. He had had pertussis at one month and measles at three years. There had been no lassitude or chronic cough. He played normally and with plenty of vigour.

Family history. The mother and father and five other children were alive and well. There was no history of tuberculosis in the family.

On admission. Weight was 48½ lb. Temperature 101·5°, pulse 130, and respirations 40. The child was well nourished and had a good colour. There was no herpes and no respiratory

difficulty. The tongue was clean. The tonsils were somewhat reddened and slight hypertrophic. The lymphatic glands in the neck were palpable. Inspection and palpation of the chest showed nothing abnormal. The percussion note was resonant throughout. On auscultation, there was an inconstant friction rub heard over the right lower anterior chest. The breath sounds were slightly diminished over this area. There were no ràles or tubular breathing. The heart and abdomen were normal.

Course. The friction rub became very definite over the right lower chest, with the appearance of a few râles and rhonchi, on the fourth or fifth day following admission. The fever of 101° for one day had dropped to 99·5° on the third day and was normal thereafter. The pulse and respirations also reached normal in three days. The rub had disappeared ten days after admission. The throat and nose were negative for diphtheria. 0·1 mgrm. of old tuberculin intradermally was negative, as was also 1 mrgm. X-ray of the chest was negative. Blood examination showed 10,000 leucocytes (59 per cent. polymorphonuclears; 33 per cent. lymphocytes; 2 per cent. transitionals; 2 per cent. eosinophiles; and 4 per cent. mononuclears). The urine was negative. The child gained 1 lb. in weight while in the hospital and made an uneventful recovery after having been treated only symptomatically, as was also done in the first case.

Discussion.

The pleura may become infected via the blood, lymph, or by direct extension. The ordinary dry, or plastic form of pleurisy may arise from various causes and be a part in the course of several diseases. The most typical form occurs in lobar pneumonia and Holt and Howland[1] in observing 398 hospital cases of pneumonia, noted 27 or 6·8 per cent. which could be classed as pleuropneumonia, the diagnosis being confirmed at autopsy or operation. Acute rheumatism in childhood may be complicated with pleurisy in 4 per cent. of the cases. Various forms of trauma to the chest wall resulting in fractured ribs may produce a local pleurisy, but many accidents to the chest wall can occur without any pleurisy resulting. Dry pleurisy in children is sometimes manifested in the specific fevers, especially typhoid, measles, and scarlet fever; occasionally it complicates a nephritis or a pyogenic infection; finally it may result as the extension of an infectious process involving the chest wall, pericardium, lung, spine, or diaphragm. Extension from the latter two points is usually considered to be tuberculous in origin.

Tuberculosis of the pleura is generally considered as not primary, but secondary to tuberculosis in the lungs or hilum lymph nodes (Miller[2]). The role of a tuberculous process in the causation of plastic pleurisy is summed up by Carmichael[3] when he states that it is practically agreed that a dry pleurisy, in the absence of disease in adjacent tissue, or specific fevers, is due to a tuberculous infection to the same extent that a pleurisy with effusion is considered tuberculous. Robert C. Patterson[4] thought tuberculosis to be so frequently the ætiological factor concerned, that it was safe to consider every pleurisy as tuberculous unless there was some other definite cause. Roughly, pleurisies with effusion are considered as tuberculous in 50 to 75 per cent. of cases. Primary pleural effusions due to the pneumococcus are said to occur in children without the co-incidence of the usual accompanying pneumonia[3]. Nobel[5] in his observations at the University Children's Hospital in Vienna on 78 cases of pleuritis in children, concluded that almost all of the cases, with the exception of a few in which a definitely different ætiology could be demonstrated, were of a tuberculous origin. However, he regarded the prognosis as very favourable,

According to Acuna, Casaubon, and Macera[6] dry pleurisy occurring in smaller children and infants is rarely of a tuberculous nature but is usually pneumococcal as would be expected from the high incidence of pneumonia in infancy. They also considered influenza as a common cause in infants. But Levin[7] diagnosed pleurisy with a rub in only one case out of 293 cases of influenzal pneumonia observed during the 1918-19 wave of influenza in the United States. He noted fifteen cases of pleurisy in influenza uncomplicated by a pneumonia, or a total of 3·7 per cent. of the non-pneumonic cases. In the 1920 epidemic, he observed no cases of pleuritis except in those cases in which an influenzal pneumonia existed, a total of seven out of sixty-one cases. The higher incidence of evident pleurisy in the 1920 epidemic was in his opinion due to the fact that there was more fibrin in the pleuræ in the 1920 cases than in the 1918 epidemic. Talbot[8] reported 31 cases of influenza in children in 1918 with no mention of a pleuritis. Howard[9] also reported 70 cases of influenza in private practice in 1918 with no evidence of a pleurisy in any of them.

Signs and Symptoms. Only very brief mention will be made of the signs and symptoms of plastic pleurisy since they are generally familiar. Usually the onset is an abrupt one with pain in some part of the chest. It is most commonly noticed about the costal margin if the pleurisy is pneumococcal, a result of the more frequent basal position of pneumonia. Tuberculous cases on the other hand, tend to be more commonly apical in type. The pain is definitely made worse by coughing or deep respiratory excursions. Dry cough is present at the onset and usually a fever of 101° to 102° with some prostration. The rub is probably more often absent than present, and is certainly often very transient in character. Respiratory excursions are apt to be short and shallow, *i.e.*, guarded in character. The duration of the fever, the rub and other symptoms depends upon the underlying ætiological factor. In pneumococcal cases with a coincident pneumonia, symptoms may exist from two days to two months, the shorter period being more common.

In the typical case of dry pleurisy where the pleura is alone affected, one naturally expects to find little or no evidence clinically except fever, the presence of pain in the chest which is aggravated by deep breathing, and perhaps a friction rub. However, in so-called pleuro-pneumonia in which more of the parenchyma of the lung is affected, the physical signs of a pneumonia will be in evidence, *i.e.*, dullness, tubular breathing, diminished air entry ; in addition a leucocytosis is practically invariable to an extent of more than 15,000 in primary croupous or lobar pneumonia, in which pleurisy as a complication is much more likely to be found.

The signs and symptoms to be expected in a case of tuberculous origin are similar to the above, but there is usually a history of lassitude, anorexia, and variation in or diminution of weight in the child. A family history of tuberculosis may be obtained. Fishberg[3] has stressed the diagnostic value of an enlarged gland at the inner end of the clavicle, under the sternomastoid, in cases of tuberculous pleurisy.

Differential Diagnosis. It is necessary to bear in mind several possibilities when confronted with a child presenting the signs and symptoms of an acute

dry pleurisy. Pneumonia and tuberculosis certainly stand in the foreground. Since it is reckoned that a tuberculous pleurisy is usually secondary to pulmonary and secondary hilum glandular involvement, an X-ray examination of the chest for hilum adenopathy, calcified foci, or parenchymal changes, is likely to reveal a lesion. A negative tuberculin test consisting of the intradermal injection of 0·1 c.cm. followed by 1·0 c.cm. of one in one thousand old tuberculin, can be taken as proof of the non-tuberculous nature of the pleurisy. A strongly positive reaction can be taken as fairly conclusive proof of its tuberculous nature in the absence of any other definite cause such as pneumonia. A negative family history and a negative history in the child as regards lassitude and inconstant weight, all weigh heavily against tuberculosis as the cause.

In the pneumococcal cases, there are usually enough physical signs in the chest to warrant the diagnosis of pneumonia, but it is of course possible that the pneumococcus may be the real cause even in cases which show no clinical signs of pneumonia, since it is known that the pneumococcus may cause a pleurisy with effusion in children without any demonstrable lung signs. In the first class of case the pleurisy is secondary to the underlying lung lesion, in the second the condition can be regarded as a primary pneumococcal pleurisy.

The location of the pleurisy may give some aid, those of a tuberculous nature usually occurring in the apices or interlobar spaces while the pneumococcal forms are usually basal. The presence of tuberculous bone or glandular disease would be suggestive. With no evidence of tuberculosis or pneumonia, it must be borne in mind that other conditions may cause pain in a similar region of the body, such as herpes zoster, pleurodynia, intercostal neuralgia, rheumatism, and diseases of the chest or spine. A careful history and physical examination will serve to distinguish these conditions from a dry pleurisy.

In the cases reported above the repeated negative tuberculin tests, the negative X-ray examination of the chest, the negative past history in the child with the negative family history, the absence of lassitude or loss of weight ; but rather a rapid gain in weight, associated with freedom from any symptoms whatever, all serve to rule out tuberculosis. Again, the absence of physical signs in the lungs (tubular breathing, dullness, crepitant râles, and flattened percussion note), the absence of leucocytosis, the negative X-ray evidence of consolidation, absence of herpes and of the typical onset of a pneumonia, the length of time during which the friction rub persisted after the fever had gone, and the very rapid return of the temperature pulse and respiration to normal, combine to exclude pneumonia as a cause. There was no evidence of rheumatism, disease of the spine, or of any of the specific fevers. If judgment were based upon the commonly accepted dictum that any pleurisy occurring in the absence of disease of adjacent tissues or in the absence of specific fevers, is a tuberculous one, then cases here presented would certainly be considered as tuberculous ; but the clinical observations and the X-ray and tuberculin tests do not allow of such a diagnosis ; and it is therefore definitely suggested that they are non-tuberculous.

Since the influenza epidemic was occurring at the time these cases were observed, it is possible that this may have been the ætiological factor concerned.

Conclusions.

1. Two cases of acute dry pleurisy in children are reported.
2. Evidence is presented against their being of a tuberculous origin.
3. In the absence of any accompanying pneumonia, influenza is suggested as a possible ætiological factor.

I wish to express my gratitude to Dr. Geoffrey Bourne for his suggestions in the preparation of this paper and for the use of the cases from his hospital service.

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PULMONARY EMBOLISM IN CHILDHOOD

BY

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Pulmonary embolism in childhood must be an event of extreme rarity, as judged by the number of recorded cases. The following case, which presents several unusual features, appears, therefore, worthy of record.

E. W. B., a male child, aged 9 years, had always enjoyed good health, with the exception of an attack of scarlet fever in 1926. On June 24th, 1929, he went to bed about 10 p.m. apparently perfectly well. He slept with two older brothers. About 1 a.m. on the 25th, a brother noticed that the boy was shivering and cold. About 1.30 a.m. he vomited and complained of thirst. He vomited again at 3.0 a.m. At 5.0 a.m. he was observed to be very pale, but asleep and breathing in a normal fashion. At 9.0 a.m. his mother went to him and found him lying on his back in bed. She noticed that he had some yellowish discharge round the mouth and nostrils, and that the bed had been soiled. She wiped away the discharge from the mouth and nose, and as he did not reply when spoken to she thought that he was merely asleep. At 10 a.m. his condition was unchanged, and there was more yellowish fluid being discharged from the mouth and nose. He was pale in the face but appeared to be breathing regularly. As his mother could not rouse him she took him to the Children's Hospital.

On admission to hospital he was profoundly unconscious and died about half an hour later.

An autopsy was performed about six hours after death. The body was that of a well-nourished boy. The thyroid gland was slightly enlarged. The thymus gland weighed 30 grm. and appeared healthy on section. The pleural and pericardial cavities presented no pathological changes. The visceral layer of the pericardium was slightly thickened and opaque, and there were many sub-epicardial petechial hæmorrhages over both anterior and posterior aspects of the heart. There was a large amount of firm ante-mortem clot of an opaque greyish-white colour in the right heart. This thrombus was firmly adherent in one place only, namely, the right auricular appendage, where it was in fact so adherent that it could not be removed without tearing. From this place of origin the thrombus extended through the right auricle, through the tricuspid valve, through the right ventricle and pulmonary valve into the pulmonary artery. It finally terminated in each pulmonary artery just distal to the bifurcation. The thrombus lay entirely free in the artery. There was no endocarditis in either the right or left side of the heart. Both the left auricle and left ventricle contained some agonal clot. On examination of the cut edge of the heart muscle the outer fringe of both the right and left ventricular wall showed changes of cloudy swelling for a depth of approximately $\frac{1}{8}$-inch. The terminal portion of the thrombus in the right pulmonary artery had become dislodged and infarcted in the lower lobe of the right lung. The infarct measured about 3 in. in diameter and was rather globular than triangular in shape. It was very hard in consistence: on section it was blackish-red in colour with its margins sharply defined. There were practically no changes to be detected in the over-lying pleura. There were no other infarctions. The brain and abdominal viscera were healthy. There was no thrombosis of any of the venous sinuses within the cranial cavity, and no evident sepsis in the ears, accessory sinuses, tonsils or teeth.

Discussion.

It is recognized that pulmonary infarction may arise without the production of any of the classical symptoms. In this case it is not possible to say when the infarction actually occurred, but it seems reasonable to presume that when it did occur the pleural and general shock that ensued caused rapid and

complete loss of consciousness. The yellowish discharge from the mouth and nostrils noticed by the child's mother, was œdematous fluid from the lung, yet death was not due to asphyxia.

As stated previously, the incidence of the condition must be extremely low and such cases as have been recorded were encountered mostly in infants. In 1905, Pehu and Horand[1] reported a case in a child aged 6 years, the condition following an aural infection. A similar case in a baby of 7 months was recorded by Guillemot[2] in 1906. In 1913, Lutz[3] reported six cases, all due either to purulent otitis media or sinus thrombosis. A case in a child aged 4 years was reported by Wessen[4] in 1921, and last year Stulik and Rust[5] reported a case in an infant of eleven months, probably due to venous thrombosis in the lower extremities. Thus, of the ten recorded cases seven were in Germany, two in France and one in America. In all these some obvious source of infection appears to have been present.

Thrombosis may arise from a variety of causes. Changes in the composition of the blood, changes in the vessel walls, and mechanical factors causing a disturbance of the circulation are the most important ones. Of these, the third is most frequently met, *e.g.*, the cardiac thromboses that occur in auricular fibrillation and myocardial failure ; but in childhood this condition is so rare that it does not need further consideration. Changes in the endocardium must therefore take first place, and these changes can only result from inflammation. A review of the macroscopical autopsy findings in my case shows that the epicardium was the seat of a very early acute inflammation, just beginning to involve the myocardium. The distance from the epicardium to the endocardium, that is, the thickness of the heart wall, is least in the auricles, particularly in the auricular appendages, where too the circulation is less strong. By far the most frequent cause of acute infection of the cardiac structures in childhood is acute rheumatism, and, further, this infection may be more virulent and more rapidly fatal than is perhaps generally recognized. I have, for instance, notes of another child, aged 5 years, who died of an acute and extensive rheumatic pan-carditis, with visible endocarditis, after a history of only 36 hours illness.

Blumer[6] states that all forms of thrombosis are exceedingly rare in rheumatic fever and that cardiac thrombosis, apart from that occurring with a complicating endocarditis and arterial thrombosis, is almost unknown. It is my opinion, however, that the cause of the infection in the case reported here was the streptococcus rheumaticus, but this cannot be definitely established as, unfortunately, no histological examinations were made.

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CONGENITAL CARDIAC DISEASE IN IDENTICAL TWINS.

BY

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The study of rare diseases and rare abnormalities is of more value in throwing light upon pathological or physiological processes than in furnishing guidance for future encounter with the same condition. This principle applies to the study of diseases in the individual, but it applies even more in the case of homogeneous twins, for here the solutions of embryological problems may become apparent, and a means is afforded of investigating the influence of the various factors which control development in childhood. The rôles of nurture and nature in directing character formation have thus been investigated by Galton[1]. The occurrence of acquired disease, both physical and psychical, in homogeneous twins has elucidated the close similarity of intimate structure and defence mechanisms possessed by such twins. In this connection, twins suffering from lienteric diarrhœa have been recorded by Cockayne[2], while asthma occurring in both of a pair has been described by Trousseau[3]. Cases of congenital abnormalities occurring doubly in twins have been investigated and recorded by Cockayne[2], who found such abnormalities involving not only gross and intimate structure but mental and metabolic processes also.

The rarity of congenital cardiac abnormalities in twins, and the writer's recent observation of twins suffering from patent ductus arteriosus, have prompted an investigation of cardiac defects occurring in paired offspring, and specially a consideration of the clinical manifestations of patent ductus arteriosus in infants. This paper therefore deals first with congenital cardiac disease in homogeneous twins, an account being given of cases recently observed, and secondly with the symptoms of patent ductus arteriosus. In the latter part other examples of this defect occurring solitarily in single children have been collected for their clinical value, and the syndrome has been described.

Cases of congenital cardiac defect in twins.

I. Debreuil-Chambardel[4] describes transposition of viscera occurring in one of twins. In weight, size, general appearance, and in the development of varicosities on the legs, these twins were identical, but one of them was discovered to have the apex beat within and below the right nipple, while X-ray confirmed the dextrocardia and showed the liver to be on the left of the abdomen. Although these findings were not conclusive evidence of transposition of the heart, the following embryological considerations make this probable. First, it is known that in double monsters the aorta bifurcates, the left branch passing backward and to the left in the normal manner in the left-sided twin ; while

the right branch passes backward and to the right in the right-sided twin. Secondly, in such monsters, transposition of the viscera has been shown by Martinotti and by Lochte to depend upon persistence of the right omphalo-mesenteric vein, and they have found that secondary rotation of the heart is usual but not inevitable. If we regard identical twins as separated double monsters, the application of these principles to such twins becomes apparent. A mirror-image hare-lip, right on one twin and left on the other, strengthens the probability that the transposition of the heart was present in one of the pair.

II. Pezzi and Carugati[7] give an account of adult identical twins both of whom had dextrocardia and probably complete transposition of viscera. While serving in the war one of the twins had a bout of malaria, and a mass in the left hypochondrium was thought to be the spleen, but was found by radiography to be the liver. Further X-ray examination showed the heart and stomach to be on the right, and the liver on the left in both of the twins. Electrocardiography showed a reversed but otherwise normal tracing in lead I; lead II was as a normal lead III, and lead III as a normal lead II.

The interest in this case lies not so much in the presence of similar visceral abnormalities but in the absence of a mirror-image dextrocardia in one twin corresponding with a normally placed heart in the other. For in this case, the external evidence indicated homogeneity in the twins, while the electrocardiographic changes said by Abbott[8] to be diagnostic of congenital dextrocardia with *situs inversus* were present. Further, the fact that this form of congenital dextrocardia is, unlike that without *situs inversus*, not of clinical significance, suggests that the former abnormality was present in the case of these soldiers.

III. The following cases of patent ductus arteriosus occurring in each of a pair of twins recently came under observation at the Middlesex Hospital. These infants were of the same sex and very similar in general appearance, size and weight. The first was admitted, at the age of 17 days on February 25th, 1929. The child was the second of the pair, and had been a full time breech presentation. There was a history that the child had been coughing for a week and that for three days before admission his condition had been worse. It was also complained that the infant went blue when coughing, and that the feeds were being vomited. On examination the infant was found to be rather emaciated and of greyish complexion. No murmur was heard on auscultation, nor were any other signs of cardio-vascular abnormality detected. The breath sounds were weak, and fine sibilant rhonchi and râles were heard throughout the lungs. For three days after admission the vomiting continued, and attacks of cyanosis occurred seven or eight times in the day. In these seizures the colour would suddenly turn to greyish blue while the breath was held. No convulsions occurred, and to all appearances the child was moribund. The administration of oxygen, and holding the infant up by the legs, brought these attacks to an end within two or three minutes. After three days the attacks became less frequent, vomiting stopped and the general condition greatly improved; on the eighth day after admission, a more severe attack than ever occurred, the breathing was never properly re-established and death took place

eight hours later. At necropsy the ductus arteriosus was found to be patent so that a probe could easily be passed from the aorta into the pulmonary artery. Evidences of bronchitis and broncho-pneumonia were found in the lungs.

The twin brother of the patient just described was admitted to the Hospital on March 6th, 1929, at the age of 26 days. For several days there had been slight cough, but two days prior to admission the cough became worse and the child began to vomit his feeds. On the day before admission cyanosis after coughing and unduly hurried respirations were observed. On examination the infant looked ill and grey. No murmur or other sign of cardio-vascular defect was observed. Signs of bronchitis were found in the lungs. Attacks in every respect similar to those in the first case were observed in this child at intervals for three days, and improvement resulted from the same treatment. However the attacks recurred on the fifth day after admission and death followed in an attack two days later. At necropsy a patent ductus arteriosus was found exactly like that observed in the other twin. Signs of bronchitis and broncho-pneumonia were also present.

Patent ductus arteriosus in infancy.

In view of the pronounced and distinctive clinical manifestations in the twins described above it was thought worth while to collect some other instances of patent ductus arteriosus in infancy. In 1911, E. W. Hall[9], at the Middlesex Hospital, described three such cases, and gave an account of their clinical course and post-mortem findings. In each instance there were observed at variable intervals spontaneous attacks of apnœa with cyanosis, death occurring as the immediate consequence of a severe or prolonged attack, and in each infant also patency of the ductus arteriosus was the sole abnormality found at necropsy.

The association of variable cyanosis and apnœic attacks with patency of the ductus arteriosus is exemplified further in the following case. A baby of four weeks was admitted to Great Ormond Street Hospital on account of blueness and difficulty in breathing. These symptoms had been variable and not noticed as a marked feature in the first few days of life. The infant wasted after birth, and four days before admission a diagnosis of broncho-pneumonia had been made in view of the respiratory symptoms. On admission he was a blue baby. There was slight pyrexia, but no definite signs were found in the lungs; the heart was rapid but no murmurs were heard. The variation in the depth of cyanosis was sufficiently great to lead to a tentative diagnosis of patent ductus arteriosus. Just before death, which occurred five days after admission, a few moist sounds were heard at both bases. At autopsy the ductus arteriosus was found to be open and was about a quarter of the bore of the pulmonary artery. There was no other abnormality of the heart, but both lungs showed broncho-pneumonia of the lower lobes.

The similarities between the four single cases described and the author's pair are (1) the absence of physical signs in the cardiovascular system: (2) the presence of patent ductus as a solitary cardiac defect: (3) the occurrence

of attacks of cyanosis with arrest of the breathing, these attacks sometimes ceasing spontaneously, sometimes yielding to oxygen or the injection of cardiac stimulants, and frequently terminated in death.

Some obscurity surrounds the mode of production of cyanosis in these patients. The most likely explanation seems to be a change in the blood supply to the lungs brought about by a reversal of the direction of flow through the patent ductus arteriosus. If blood normally passing from the right ventricle into the pulmonary circuit is deflected through such an abnormal passage into the systemic circulation, progressively increasing cyanosis must follow. Supposing this to be the origin of the cyanosis, it remains to explain the cause of the deflection of blood from the pulmonary to the systemic circuit, and the frequent termination of the attack with resumption of normal conditions.

The most probable causes of increased resistance in the pulmonary circuit are any muscular effort on the part of the child, particularly crying or coughing, and engorgement of the pulmonary capillaries as occurs at the onset of pulmonary infections. A history of cough preceding the onset of cyanotic attacks is found in two of the cases described in this paper, and in these, as in one other case, broncho-pneumonia was found at autopsy. In the remaining three cases no such history was obtainable, nor was any pulmonary lesion discovered post mortem. Assuming reversal of blood-flow in the ductus to be the cause of cyanosis, the same cause in an opposite direction must operate in terminating the attack. This reversal might well be explained by the rise in arterial blood-pressure which accompanies asphyxia.

How it is that no murmur is presented by these patients, while the classical "mill-wheel" murmur is typical of patent ductus arteriosus in the adult, is not clear. It has been suggested that the difference depends upon the anatomical nature of the communication; if the ductus is straight and of uniform bore (as in all the cases here described) no murmur is produced, while a spindle-shaped dilatation of the channel which is not uncommon in the adult may be responsible for the continuous diminuendo and crescendo bruit.

For permission to use notes on patients under their care, I am indebted to Dr. C. E. Lakin and Dr. E. A. Cockayne, Physicians to the Middlesex Hospital, and to Dr. Robert Hutchison, Physician to the Hospital for Sick Children, Great Ormond Street.

Summary.

1. Three cases of congenital cardiac defect affecting one or both of twins are described. Two of these are taken from the literature; the third instance in which patency of the ductus arteriosus existed as a solitary cardiac defect in both of the twins is here newly recorded.

2. The clinical course and pathological findings in the author's cases are described, and reference is made to the manifestations observed in other cases of patent ductus arteriosus occurring as a solitary abnormality in infancy.

3. The origin of congenital defects in twins is discussed.

4. The symptoms corresponding to patency of the ductus arteriosus, and the probable mode of production of the syndrome are outlined.

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CHANGES IN THE BLOOD CHEMISTRY IN CONGENITAL HYPERTROPHIC PYLORIC STENOSIS AND THEIR CLINICAL SIGNIFICANCE.

BY

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A fairly extensive literature is accumulating regarding the clinical symptoms and chemical findings in cases of high intestinal obstruction, and particularly when the obstruction is situated at the pylorus. Hartmann and Smyth[1] have recently published an exhaustive report of a series of investigations in infants suffering from vomiting due to various causes. More observations, however, have been made in the adult, but the bulk of the published work is a record of the study of the condition as experimentally produced in animals.

In 1918, McCann[2] showed that the plasma CO_2 combining power of the blood was greatly increased after experimental obstruction of the pylorus. Two years later, McCallum[3] and his co-workers demonstrated the same phenomenon and indicated its association with a fall in the chloride content of the blood. This they explained as being due to loss of chloride by the vomiting of the gastric juice which in turn led to an increase of the plasma CO_2 to make good the deficiency of acid radicles. These same investigators found that the onset of tetany, which invariably occurred, could be prevented by intravenous administration of sodium chloride. Hastings, Murray and Murray[4], Haden and Orr[5] and Gamble[6] have also published papers throwing further light on the condition. Brown, Eusterman, Hartmann and Rowntree[7] described similar chemical findings in duodenal obstruction in the adult and Ellis[8] demonstrated the presence of alkalæmia in two cases of intestinal obstruction. An identical picture was shown to be present in cases of duodenal ulcer after intensive alkali treatment especially in the presence of impaired renal function (Hardt and Rivers[9]).

In the present communication we wish to record the observations both clinical and chemical made during a study of congenital hypertrophic pyloric stenosis extending over the past four years. It is obvious that because of the age of the patients and the severity of the condition, the investigations had of necessity to be less complete than desired. In all, over fifty cases were studied but we propose to give only such details as are relevant for correlating the various findings.

Before we proceed to analyse our results, it will be of advantage to give a brief resumé of these findings which, on the whole, are in accord with those of other workers. A most striking and probably the only important clinical manifestation of the presence of an alkalosis in these cases is the depressed breathing. This may be evidenced in one or more of the following three ways. First, there may be a shallow type of respiration, so shallow in fact that even with the bell of the stethoscope placed in front of the nose and mouth, it is

often very difficult to hear the respirations. Secondly, the rate is frequently diminished, often to six or eight times per minute, and thirdly, there are well-marked and often alarming periods of apnœa followed by three or four shallow respirations producing a typical Biot type of respiration. Most often, all three manifestations are present at the same time. At this point we would mention that we believe this condition to be present at some time in practically every case of pyloric stenosis in infancy. Coupled with this respiratory depression there exists a general lethargy, giving one the impression that the infant is under the influence of a hypnotic drug. In one instance, a baby was brought to hospital because the mother had noticed undue quietness. Recognition of the depressed breathing raised the suspicion of pyloric stenosis although the infant had not vomited on any single occasion. On examination typical gastric peristalsis was evident together with a palpable pyloric tumor. The diagnosis of pyloric stenosis was ultimately confirmed post mortem by the presence of a hypertrophied pylorus.

The biochemical examination of the blood shows usually a decrease in chlorides and an increase in the total CO_2 content and, less frequently, in the non-protein nitrogen. As a rule, these three findings are present together but the variations from the normal in each are not necessarily of the same degree. Table I gives some results which will serve to indicate this variation. In several cases, the fixed base of the serum was also determined (Table 2), and it will be seen that it is usually within normal limits (149—162 mM per litre) although occasionally it is slightly reduced.

TABLE 1

GENERAL BIOCHEMICAL FINDINGS IN THE BLOOD IN PYLORIC STENOSIS.

Name	Age in weeks	Total CO_2		Chlorine (Cl)		Non-protein nitrogen mgm. per cent.	Excess non-prot. nitrogen (mM. per litre)	CO_2 + Cl (mM. per litre)	CO_2 + Cl + excess N.P.N. (mM. per litre)	Respir. rate (per min.)
		Vol. per cent.	mM. per litre	mgm. per cent.	mM. per litre					
R. C. ...	8	140·5	63	140	40	46	2	103	105	18
N. R. ...	4	140·0	63	180	51	80	8	114	122	16
A. M. ...	8	83·1	37	210	60	32	—	97	97	40
W. G. ...	6	85·0	39	190	54	35	—	93	93	24
M. M. ...	12	62·5	28	330	94	60	5	122	127	40
M. A. ...	8	125·6	56	110	31	145	20	87	107	—
A. W. ...	7	110·2	50	170	49	63	5	99	104	26
E. M. ...	8	100·5	45	160	46	86	9	91	100	12
J. K. ...	6	91·8	41	160	46	50	3	87	90	24
J. McK. ...	8	112·0	50	220	63	32	—	113	113	—
A. C. ...	3	113·0	50	240	69	34	—	119	119	10
G. H. ...	7	95·8	43	190	54	75	7	97	104	14
W. A. ...	3	103·7	46	300	86	38	—	132	132	—
W. A. ...	4	148·0	66	130	37	183	27	103	130	—

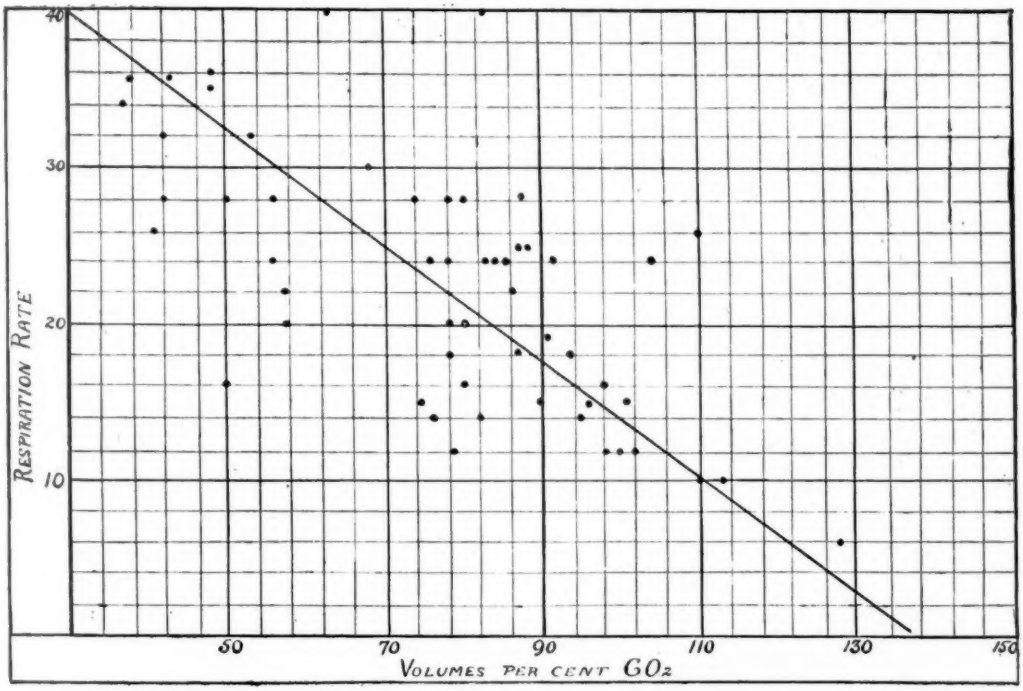
TABLE 2.

SHOWING RELATIONSHIP BETWEEN CO_2, CHLORIDE AND FIXED BASE.

Name	J.McK.	J.P.	T.S.	G.C.	W.B.	A.B.	M.McP.	D.F.	R.S.	E.F.
CO_2 (mM. per litre)	51	53	56	21	50	54	28	49	45	46
Cl (mM. per litre)	63	54	—	70	—	34	83	—	—	60
Fixed base (mM. per l.) ...	144	151	150	160	159	152	154	153	143	161

CHART I.

Showing Relationship between Respiratory Rate and Total CO_2 Content of Blood.



Relationship of the total CO_2 Content and Respiration. One of the most striking correlations among our findings is that between the total CO_2 content of the blood and the respiratory rate. This is all the more striking when one remembers that it is the total respiratory exchange and not merely the rate of breathing which is of significance. Further, it is not the total CO_2 but rather the ratio of the free and combined CO_2, which is the regulating factor in respiration. In Chart I are plotted individual observations of the total CO_2 content of the blood against the respiratory rate at the time of withdrawal of the blood. The slower the respiratory rate, the greater is the increase in CO_2. There are certain anomalous findings on the chart but when one remembers the possibility

of tachypnœa resulting from oxygen deficiency, it can be readily understood that such results are only to be expected. In Table 3, these results are grouped into six averages which indicate clearly the strong correlation.

TABLE 3.

SHOWING CORRELATION BETWEEN CO_2 CONTENT OF BLOOD AND RESPIRATORY RATE IN CASES OF PYLORIC STENOSIS.

Group	1	2	3	4	5	6
Average respiration rate (per min.) ...	8	13·8	18·1	23·4	27·8	38·9
Average CO_2 content (vol. per cent.)	138·8	108·6	99	99	87·7	65·2

This relationship between the CO_2 capacity and slow breathing apparently only holds good in patients suffering from pyloric stenosis. During the past three years, it has been our custom to pay particular attention to respiratory rates in other conditions than pyloric stenosis, and not infrequently we have observed great reductions in rate, but in no instance was the CO_2 content of the blood raised appreciably above the normal. These findings are seen in Table 4. In the case of J.L. suffering from encephalitis with a respiratory rate of 8 per minute, the chlorides (C^1) were 240 mgm. per cent., the non-protein nitrogen was 35 mgm. per cent. and the pH was 7·25 (i.e. an acidosis). One important point in the clinical differentiation of these two types of slow breathing is the degree of cyanosis present. The cases in Table 4 invariably showed a fair degree of cyanosis while the cases of pyloric stenosis as a rule none at all. The explanation of this is not clear. Theoretically, the high CO_2 content should predispose to anoxæmia, since CO_2 shifts the oxyhæmoglobin dissociation curve to the right, that is, the more CO_2 present the less the degree of oxygen saturated, and hence the greater the amount of reduced hæmoglobin.

TABLE 4.

TOTAL CO_2-CONTENT OF BLOOD IN NON-OBSTRUCTIVE CASES WITH REDUCED RESPIRATORY RATE.

Case	Diagnosis	Respiratory rate (per min.)	Total CO_2 (vol. per cent.)
J.L.	Encephalitis Lethargica	14	56·5
,,	,, ,, ...	8	62·7
,,	,, ,, ...	8	67·0
M.M.	Cerebral hæmorrhage	10	57·5
R.M.	Prematurity	10	55·0
W.D.	Congenital heart disease	4	52·7
J.R.	Prematurity	12	60·6
J.G.	Meningitis	12	57·1
M.C.	Pyuria	18	55·4

Relationship of the CO_2 Content and Vomiting. The relationship between the total CO_2 content of the blood and the severity of the vomiting is not close. It is, however, admittedly difficult to gauge the amount of vomitus and, what is even more important, the character of the vomitus, for example, the amount of chlorine present. An attempt has been made in Table 5 to correlate these two factors but we feel that too much stress should not be laid on it. When the records of individual patients are examined, it is found that, occasionally, the total CO_2 content of the blood may remain high despite the fact that there had been no vomiting for several days prior to its estimation. This might be explained by the length of time which it takes for the blood to return to its normal composition. But in one patient, vomiting can have played absolutely no part in producing the increase in the CO_2. This was the case already referred to, who, although suffering from pyloric stenosis, did not vomit either previous to admission or during a four weeks' stay in hospital. The total CO_2 content of the blood reached the value of 102 vol. per cent., and the CO_2 dissociation curve showed clearly its increased capacity of holding CO_2.

TABLE 5.

SHOWING CORRELATION BETWEEN CO_2 CONTENT, CHLORIDE CONTENT, AND VOMITING IN CASES OF PYLORIC STENOSIS

Severity of vomiting	Nil	Slight	Moderate	Severe
Total CO_2 vol. % (average)	102·9*	77·2	97·6	103·2
Cl mgrm. % (average)	——	260	250	180

* Only two cases.

In patients suffering from vomiting, and even from severe vomiting, due to causes other than pyloric stenosis, one rarely if ever finds the CO_2 content raised. It must be remembered, however, that it is not the mere presence of vomiting but rather the nature and amount of the material vomited which is of significance. One nevertheless feels justified in concluding from a study of this series of pyloric stenosis that the severity of the vomiting is no measure of the metabolic disturbance as evidenced by the increase in the total CO_2 content of the blood.

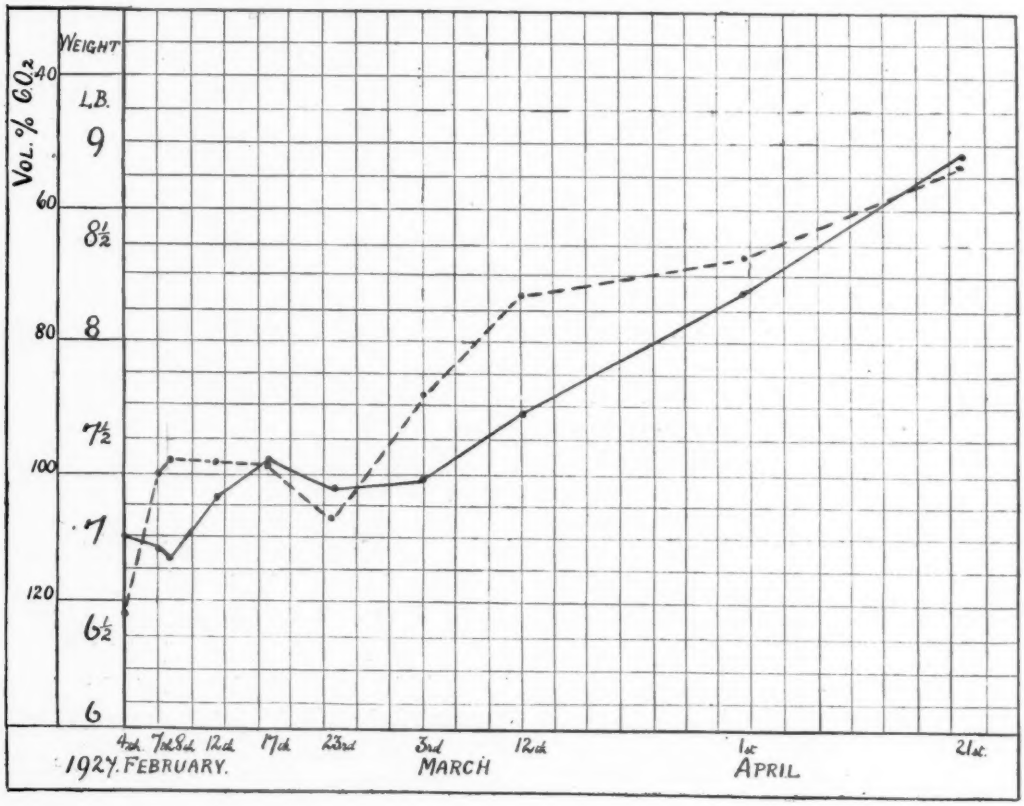
The total CO_2 content of the blood and the general nutrition. An association between the fall of the CO_2 to normal and the increase in the weight of the infant is illustrated in Chart II. This correlation holds good only for the same individual and therefore an isolated observation on the CO_2 content cannot be taken as a prognostic sign. A great increase in the CO_2 content does not necessarily mean a worse prognosis than a moderate rise. Furthermore, there does not seem to be any relationship between the level of the CO_2 and the length of time the vomiting has existed.

The association between the fall in CO_2 and the improvement in general nutrition was recognized to be simply the result of concomitant events and not dependent on cause and effect. Nevertheless, an attempt was made in a few

instances to influence the CO_2 content of the blood and determine whether such change resulted in clinical improvement. In one case, by means of transfusion, the CO_2 value was reduced from 98 vol. per cent. before transfusion to 70·2 vol. per cent. five minutes after transfusion. The donor's blood, of which 110 c.cm. were given along with 40 c.cm. normal saline, contained 62·1 vol. per cent. CO_2. Assuming the volume of the infant's blood to be 200 c.cm. (weight of infant 3·1 kilos) then 75·5 vol. per cent. represents the value one would calculate from a mixture of the two bloods and the saline. There was no apparent change in

CHART II.

To show increase in Weight and Fall in total CO_2 content of Blood in case of infant J.B.



the clinical condition of the infant and this lowering of the CO_2 content was not permanent, as within four days it had risen again to 97·8 vol. per cent. In another case, the infant's blood was withdrawn twenty hours after transfusion but the CO_2 content was practically unaltered from the pre-transfusion value. In two cases calcium chloride was given. In one the CO_2 content was reduced from 110 vol. per cent. to 62·3 vol. per cent. although the clinical condition was unchanged, while in the other, the CO_2 content was unaffected.

The CO_2 content of the blood and its reaction. The question arises whether the increase in the CO_2 content is indicative of a non-gaseous alkalosis or of a gaseous acidosis. The CO_2 dissociation curve of the blood shows a shift

to the left, *i.e.*, the capacity to hold CO_2 is increased, a finding equally characteristic of either of the above two conditions. It is obvious that if the depressed breathing is primary, the condition is one of gaseous acidosis such as occurs in subnormal activity of respiratory function. If, however, the increase in CO_2 content is the cause of the diminished respiratory exchange, the condition must be one of non-gaseous alkalosis. Ellis[8] has given details of the findings in two cases of high intestinal obstruction in both of whom there was an alkalæmia, as indicated by the pH of the blood. In a few instances in our series, the pH of the blood has been determined. The figures obtained are found in Table 6. It will be seen that if any change from the normal does occur, it is toward the alkaline side. In contrast with this finding, it is interesting to note the pH figure in the case of J.L. suffering from encephalitis. Here, although the respiratory rate was only eight per minute, the total CO_2 content was 67 vol. per cent. and the pH 7·25. This slightly increased CO_2 value and the pH on the acid side of normality indicate a gaseous acidosis. One can, therefore, conclude that in pyloric stenosis, the disturbance of the acid base balance is toward the alkaline side and that the change in the respiratory volume is secondary.

TABLE 6.

pH FINDINGS AND THE RELATIONSHIP TO CO_2 CONTENT OF BLOOD.

Name	Diagnosis	Respiratory rate (per min.)	Total CO_2 (vol. %)	pH
J.C.	Pyloric stenosis	?	140·0	7·76
R.R.	,, ,, ...	15	110·0	7·33
W.B.	,, ,, ...	?	73·2	7·35
McL.	,, ,, ...	?	53·4	7·39
M.R.	,, ,, ...	24	110·0	7·52
J.L.	Encephalitis lethargica...	8	67·0	7·25

The presence of such a degree of alkalosis as suggested by the high CO_2 values would lead one to expect the frequent occurrence of tetany. Signs of increased muscular irritability, as a matter of fact, have been reported frequently in high intestinal obstruction in the adult, as well as that produced experimentally in dogs. Convulsions, although said to be common by some observers, are in our experience rare in pyloric stenosis of infancy. In only two cases was there any such history obtained. In one of these laryngismus was an associated symptom. In no case tested was the neuro-muscular excitability increased as one might have expected. The reason for this absence of the signs of tetany may in part be due to the increased blood calcium content which we have found as high as 14 mgrm. per cent.

The cause of the alkalosis presumably is the increased amount of available base resulting from a deficiency of chlorine. It becomes necessary for the CO_2 content to rise in order to combine with this base.

Fig. I (a) adapted from Gamble's paper shows that CO_2 is one of the acid radicles combined with fixed base, the others being Cl, HPO_4, SO_4, organic acid and protein. Of all these acid radicles, CO_2 is the most mobile and elastic, being very easily retained or dispensed with by the activity of the respiratory centre. In Fig. I (b) is represented the state of affairs found in pyloric stenosis. It will be seen that the excess of CO_2 makes up for the deficit of Cl. The results recorded in Table I indicate that this balancing of diminished Cl by increase of CO_2 although generally complete is not necessarily the rule. Unfortunately, we have not obtained complete data in any one case. The figures for fixed base indicate that it is practically unchanged. Our data for acid radicles other than

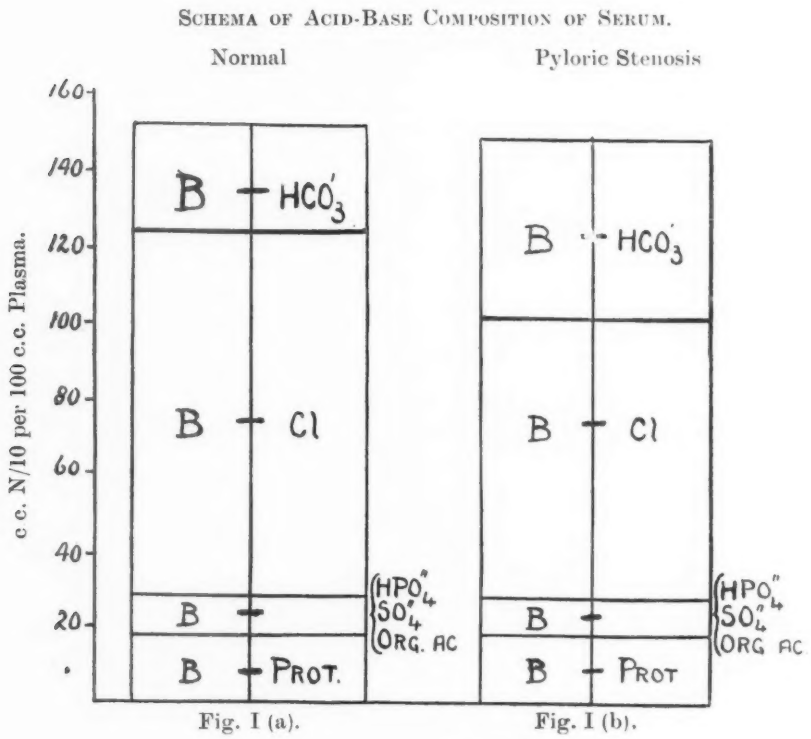


Fig. I (a). Fig. I (b).

Cl and CO_2 are scanty. In two cases we found values for inorganic phosphorus of 10·5 and 11·6 mgm. per cent. respectively. Atchley and Benedict[10] maintain that they can demonstrate an increase in the phosphate, sulphate and protein of the blood sufficient to account for the diminution in the ($Cl+CO_2$) value. Gamble[6] postulates an increase in organic acid. The ketone content of the blood has not been estimated in this series but frequently we have noted a fair degree of ketonuria. This may be consequent on the inanition (starvation), or due to alkalæmia or to both factors, and it is quite probable that these ketone acids take part to a certain extent in the compensation for the diminished $Cl+CO_2$ content.

The behaviour of the chlorides:—The fall in the blood chloride is one of the most constant changes in the biochemical findings. The reduction seems to

bear some relationship to the severity of the vomiting (Table 5), even although this relationship is masked by the inability to determine the actual amount of vomitus and its chloride content. The urine contains but a trace of chlorine, which is to be expected if chlorine is a threshold substance. Following the intravenous injection of a solution of normal saline practically all the water is excreted whereas approximately 80 per cent. of the chlorine is retained. In infants suffering from vomiting from other causes, only about 10 per cent. is retained. These results are shown in Table 7. In the two infants who were vomiting from causes other than pyloric stenosis, the amount of Cl retained was 11·8 and 7·0 per cent. respectively. In the cases of pyloric stenosis, 80·7 and 81·8 per cent. were retained. After operation in one case only 2 per cent. was retained which indicates that the condition was relieved. This retention of Cl in the examples of pyloric stenosis indicates definitely a chlorine hunger of the tissues. Hartmann and Smyth[1] maintain that severe vomiting may also lead to a depletion of the blood chloride. While it is true that the chloride may be somewhat reduced, it appears evident that the metabolism of chlorine in non-obstructive cases presents a different picture from that in pyloric stenosis.

TABLE 7.

CHLORIDE CONTENT OF URINE AND PERCENTAGE ABSORPTION OF CHLORIDE IN CASES OF PYLORIC STENOSIS AND NON-OBSTRUCTIVE VOMITING.

Name	Volume of urine	Amount of saline injected (cc.)	Chloride in urine		Percentage of chloride retained	Remarks
			Per cent.	Total		
W.B.	91	—	0·585	0·532	—	Feeding case.
	205	100	0·647	1·326	11·8	Vomiting+
R.W.	370	—	0·303	1·120	—	Meningitis.
	450	80	0·420	1·890	7·0	Vomiting+
J.R.	265	—	0·048	0·128	—	Pyloric stenosis.
	330	60	0·07	0·232	80·7	
C.C.	232	—	nil	nil	—	Pyloric stenosis (before operation)
	350	100	0·047	0·164	81·8	
	784	—	0·738	5·786	—	(After operation).
	920	100	0·725	6·670	2·0	

DISCUSSION.

Several views have been put forward as to the cause of the biochemical picture in high intestinal obstruction. That most commonly held is the one suggested by MacCallum[3] and elaborated by Gamble[6] and his colleagues. They believe the primary factor to be the loss of chlorine, base, and water by vomiting. This impoverishment of body chlorine is compensated for by the retention of

CO_2 with consequent production of an alkalosis. Haden and Orr[5], however, previously pointed out that a similar condition could be produced by experimental pyloric obstruction in rabbits, animals which do not vomit. But Gamble and McIver[11] were able to show that in rabbits there followed a very marked dilatation of the stomach into which the chloride was secreted and virtually lost to the body despite the absence of vomiting. This view certainly seems to explain all the experimental findings in animals. Ellis records the case of a patient suffering from carcinomatous obstruction of the pylorus with symptoms of tetany and biochemical evidence of a severe alkalæmia. There was no free hydrochloric acid in the gastric juice. The vomiting was severe, entailing in all probability a great loss of neutral chlorides. An explanation to fit this case is found in the fact that the reserve of fixed base is greater than that of chlorine so that the former is maintained at a more or less normal level in the blood while the chlorine content falls despite the fact that equivalent amounts of base and chlorine are lost in the vomitus.

In the analysis of the results in this series there is undoubtedly some relationship between the depletion of the blood chloride and the severity of the vomiting, and this in spite of the difficulty in estimating the latter factor and the great variation which is bound to exist in the chloride content of the tissues of different individuals. There is, however, one case in our series which does not permit of explanation on the basis of this hypothesis. This is the case of the infant referred to previously who did not vomit. He was admitted to the ward at the age of four weeks with the diagnosis of mental deficiency and pyloric stenosis. Visible peristalsis was readily demonstrated and there was a tumour palpable in the region of the pylorus. This infant was in the ward for four weeks and finally succumbed to a secondary infection. At the post-mortem examination, typical hypertrophic pyloric stenosis was revealed. During his residence in hospital he took his feeds well but never once vomited. He was not constipated. He presented the typical clinical picture of a severe alkalosis and the total CO_2 content of the blood was 102 vol. per cent. The respiratory rate averaged about 12 per minute. Unfortunately the blood chlorides were not estimated. It is difficult to understand how the depletion of the chloride resulted in this particular instance. It is highly improbable that the chlorine lost to the body during the four weeks' stay in hospital could have been lost *via* the gastric secretions. We have no information regarding the renal efficiency in this case.

Another hypothesis which has been advanced is that the condition is in part due to renal inefficiency. The chief evidence in favour of this view is the presence of an increased non-protein nitrogen content of the blood. At first this increase was attributed to increased destruction of tissue proteins as a result of toxæmia (Cooke, Rodenbaugh and Whipple[12]). Brown, Eusterman, Hartmann and Rowntree[7] suggested that the increase in the blood urea is the result of inefficient renal activity and concluded that the tetany-like symptoms are really uræmic in nature. In their paper they give details of the macroscopic and microscopic appearances of toxic nephritis occurring in six cases of fatal pyloro-duodenal obstruction. Ellis supported this view by his finding of a

low percentage excretion of urea despite a high blood urea, and by the fact that an alkalosis can be produced by administration of alkali only when the renal function is impaired. In one of the two cases reported by him there was pyæmia involving the kidney and in both there was noted the excretion of an acid urine (pH=5·6) associated with an over-alkaline plasma.

Hartmann and Smyth[1] have given figures which lead them to believe that the increase in N.P.N. is for the purpose of maintaining the normal osmolar concentration. They calculated the molecular value of the excess N.P.N. on the assumption that it is all urea and that two molecules of urea constitute one milli-equivalent. In Table 1 we have attempted to do the same and the findings occasionally lend some support to their view. Especially is this the case in the patient W.A. whose blood was analysed on two separate occasions. On the second occasion there was a more marked diminution in chloride with an increase in the CO_2 which did not compensate for the extra chloride deficiency. On calculating the value for the excess N.P.N. it is found that the deficiency is almost exactly balanced by the rise in N.P.N. Many of the other results, however, fail to support the view. Thus in the blood of A.M. or W.G. the decrease in the combined CO_2 plus Cl value is not associated with any increase in the non-protein nitrogen. Two possible explanations of these discrepancies suggest themselves, first in the excessive formation of ketone bodies and second, an increase in the base binding power of the proteins. Atchley and Benedict[10] have shown that owing to anhydræmia, the serum protein is increased in amount. Its base-binding power depends in addition on the pH of the medium. The more alkaline the plasma the greater is the capacity of the protein to hold base.

A third view was put forward in a series of papers by Haden and Orr[5]. They suggested that the chlorine was fixed in the tissues by some toxin and supported this view by the beneficial results obtained from the administration of chlorides. This can be equally well explained on Gamble's theory which Haden and Orr[11] in a recent paper apparently accept. Drake and Tisdall[13] have obtained similar results to those found in experimental obstruction by the injection of histamine. They found that there was no relationship between the decreased Cl content and the degree of intoxication which was, however, closely related to the concentration of non-protein nitrogen. Further they concluded that the decreased Cl content was not due to loss in the gastric secretions since apomorphine which led to a greater loss of Cl in the vomitus did not induce any diminution in the plasma Cl. Our results do not throw any light on this point.

Conclusions.

1. Pyloric stenosis in infancy is associated with an alkalosis presumably produced by a loss of the acid radicule chlorine from the body. The loss of chlorine is roughly related to the severity of the vomiting. The total CO_2 content varies inversely with the blood chlorides. The fixed base as a rule is unaltered or at the most only slightly diminished.

2. The rise in CO_2 is evidenced by a depression of the breathing (Biot type of respiration), which affords a ready method of its clinical recognition.

3. Certain cases occur which do not permit of the explanation of loss of chlorine by vomiting. It would appear that in such cases another factor, possibly impairment of renal function is present.

4. The conclusion that the rise in the non-protein nitrogen occurs in order to restore the osmolar concentration of the blood is not always justified.

We desire to express our thanks to the Medical Research Council for their help in this work.

Analytical methods used:—Blood—Total CO_2—Haldane[15]: Chloride—Whitehorn[16]: Non-protein Nitrogen—Folin-Wu method: Fixed Base—Stadie and Ross[17]: Calcium—Kramer and Tisdall's method: Phosphorus—Tisdall's method: pH—Dale and Evans[18]. Urine chloride—Volhard's method.

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